SYNTHESIS OF MEDIUM-SIZED-RING COMPOUNDS

THESIS

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by

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I wish to state that the contents of this thesis are entirely my own work carried out during the years 1957-1960 at the University of Glasgow.

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Summary

Part One:

The work discussed in this part of the thesis was undertaken with a view to synthesizing hydroxy-tropones by the ring expansion of the six-membered ring. The acid-catalysed rearrangements of the epoxides of methylenexanthrone, benzylidenexanthrone, and 2-benzylidene-1-tetralone have been studied and attempts have been made to rearrange the dibromides of methyleanthrone and 2-benzylidene-1-tetralone by means of silver oxide. None of these compounds but the epoxide of 2-benzylidene-1-tetralone smoothly rearranged by acids or boron trifluoride etherate to a seven-membered ring.

4:5-Dihydroxy-2:3-6:7-dibenzocycloheptadien-1-one first prepared by Treibs and Klinkhammer was rigorously shown to have the cis-configuration. The trans-isomer was also prepared, and the solubility of the two diols in alkali was explained by postulating a hemi-ketal structure and it is clearly not due to an o-quinonoid structure as suggested by Treibs and Klinkhammer.

Part Two:

As a model for a proposed synthesis of caryophyllene, the preparation of 1-carbethoxy-5-methylbicyclo (3,3,1) non-3-ene-9-one and its attempted conversion to 5-methyl-cyclo-oct-4-ene-1:5-dicarboxylic acid has been examined. The structure and mode of origin of two rearrangement products encountered in this work have been investigated and in the light of these results, the synthesis of 1-carbethoxy-5-methyl-bicyclo (3,2,1) oct-6-ene-8-one has been undertaken. The successful synthesis of this compound is discussed in terms of a model synthesis of longifolene.

PART ONE

INTRODUCTION

(Formula flow sheets for this section on Pages 38-50)

According to the modern concepts of aromaticity not only benzene, but all those ring systems which have (4n + 2)Π electrons should show aromatic character. This hypothesis was first put forward by Hückel' in 1931. Thus cyclopentadiene (1) carrying a negative charge and cycloheptatriene (2) carrying a positive charge should show aromatic character. From a study of the triphenylcyclopropylium ion, Breslow and his co-workers[2] predicted that the cyclopropylium cation (3) should be a fundamental aromatic system. Breslow[3] has obtained strong support for the above prediction by his study of the physical properties and nuclear magnetic resonance spectrum of dipropylcyclopropylium perchlorate.

Dewar [4,5] in 1945, first predicted that 2-hydroxycycloheptatrienone(4), which was at that time unknown and which he named "tropolone" should also show aromatic character. He suggested that stipitatic acid and colchicine might well be ~~the~~ representatives of this class of compounds. Tropolone was synthesised by Doering and Knox[6] and found to be very stable. This stability was explained by the fact that its canonical forms (5, 6) resonate with its ionic form (7) in which the seven-membered ring contains the necessary Π electrons. It is therefore a particular case of the tropylium aromatic type predicted by Hückel'.

Tropolone, in keeping with its aromatic character shows some resistance to oxidation and reduction;[6,7] e.g. it resists catalytic reduction in the presence of palladium but platinum or nickel

catalysts promote the reduction to cycloheptane-1:2-diol. Tropolone has also been found to be insensitive to perbenzoic acid[8] and performic acid[9]. Theoretical considerations led Dewar[10] to predict that tropolone should resemble phenol both in its acidity and in electrophilic and radical substitution reactions which should occur almost exclusively in the γ-position. Tropolone has a pk_a 6.97[11] at 30°, and phenol pka 10. Electrophilic substitution has been found to take place both in α- and γ-position, with the latter isomer predominating in most cases. Thus nitration is effected by dilute nitric acid and yields in the main the γ-derivative. Sulphonation could not be achieved by sulphuric acid treatment because of the conjugate acid formation (8), but tropolone could be sulphonated by sulphamic acid treatment and the product once again was the γ-isomer. Tropolone also undergoes nitrosation and diazocoupling exclusively in the γ-position, likewise the Riemer Tiemann reaction gives the γ-formyl and γ-carboxyl tropolones[12].

The only free radical substitution reaction investigated[13] was the Elbs persulphate oxidation of β-methyltropolone and in this case also the main product is the γ-hydroxy substituted product.

The reactivity of substituted tropolones reflects this aromaticity of the tropolone ring system: e.g. nitro, -, nitroso -, and azo-, tropolones can be reduced to the corresponding aminotropolones. γ-Aminotropolone can be diazotised and sucessfully subjected to the Sandmeyer, Skraup or Doebner - Von Miller reactions[12]. The foregoing properties amply confirm the aromatic nature of tropolone and as previously explained, the aromaticity must stem from the contribution of the tropylium ion structure.

Two conclusions can be drawn from this evidence; firstly, the position of the hydroxyl group should not alter the nature of the molecule and hence 3- and 4- hydroxytropones (9,10) should show aromatic character. Secondly, it should be immaterial whether there is any hydroxyl group in the molecule or not, that is, tropone (11) should itself show aromatic character. Work in progress, in this laboratory has been directed towards the investigation of the above two deductions and this work describes attempts to prepare substituted 4-hydroxytropones.

Tropone derivatives are not easily prepared in the laboratory, the yields in many cases have proved to be very poor, [14,15,16,17] 3-Hydroxytropone has been prepared by Johns et al.[18] and 4-hydroxytropone has been synthesised by Nozoe[19] and Coffey[20] but the routes used were somewhat tedious.

Since tropone and 3- and 4- hydroxytropones were not readily available, 2:3-benzotropone (12), first prepared Buchenmeser[21], has been used to study the aromaticity of the seven-membered ring[22]. Lockhart[23] reported an improved method for the preparation of this compound and examined the reactions of 2:3-benzotropone for evidence of the aromatic character. Although 2:3-benzotropone did give derivatives with reagents which normally effect substitution in aromatic compounds, it was shown[22] that these proceeded by an addition elimination-type reaction and it has been suggested by Lockhart[22] that 2:3-benzotropone should be regarded more as a normal poly-unsaturated ketone.

However, it has been found that the 4-hydroxy-(13) and 7-hydroxy-

2:3-benzotropone (14) prepared by Buchanan[24] and Cook[25] respectively were readily substituted in the seven-membered ring by electrophilic reagents. The presence of a hydroxyl function somewhere in the tropone ring would therefore appear to be a prerequisite of the aromatic character. It was therefore considered of interest to compare the reactions of 2:3.6:7-dibenzotropone (15) and its 4-hydroxy derivative (16). In an attempt to synthesise the hydroxytropone (16) Buchanan[26] was unable to form the epoxide of 2:3,6:7-dibenzotropone (15). Treibs and Klinkhammer[27] have reported that hypochlorous acid failed to react with this tropone (15), although bromine could be added to the 4:5-carbon-carbon double bond. The presence of two flanking benzene rings appeared to suppress the reactivity of the isolated double bond in this compound. Buchanan[28] also attempted to prepare the hydroxytropone (16) by dehydrating the diol[27](17) but has only been able to isolate anthrone (18).

Cook[29,30] has reported the preparation of 4-phenyl-5-hydroxy-2:3,6:7 dibenzotropone (21) by the route shown in Scheme A. The benzylidene derivative (19) of anthrone (18) on bromination gave the dibromo derivative (20) which on treatment with moist silver oxide furnished the required compound (21) by a carbonium ion rearrangement. 5-Phenyl-4-hydroxy-2:3,6:7 dibenzotropone (21) so formed was a crystalline compound. It gave a semicarbazone and also an acetate which indicated the presence of both tautomeric forms (21 & 22).

The experimental proof of the structure of the hydroxytropone (21) is based on the fact that it gave on oxidation 2-benzoylbenzophenone-2'-carboxylic acid (23) which on dehydration was converted into the

spiro[cyclic]lactone (24), the structure of which was established by its synthesis from ethyl benzoate and magnesium o-tolyl bromide as shown in scheme B. The conversion of the acid (23) into the spiro[cyclic] lactone (24) is undoubtedly due to the acid being in equilibrium with the hydroxyphthalide (25), a phenomenon exhibited by ketonic acids of benzophenone o-carboxylic acid type. Further confirmation of the structure of the spiro[cyclic]lactone was furnished by its reduction to 9-o-carboxyphenylanthrone and 9-o-carboxyphenylanthracene.

Although Cook's experimental evidence is consistent with the postulated structure (21), he failed to isolate any compound containing a seven-membered ring during his structure determination.

The present work was undertaken with a view to providing further structural proof for 5-phenyl-4-hydroxy-2:3,6:7-dibenzotropone (21) by an unambiguous route which might be flexible enough to afford the corresponding 4-hydroxy-2:3,6:7-dibenzotropone (16).

DISCUSSION.

From the foregoing discussion, the apparent method of preparing 4-hydroxy-2:3-6:7-dibenzotropone (16) would be to treat methylene anthrone dibromide[31] (27) with moist silver oxide. However when this reaction was carried out only - 'bianthronyl[32] (28) was obtained. It should be noted that methyleneanthrone dibromide loses hydrogen bromide even on treatment with wet acetone.

It is evident that Cook's synthesis of 5-hydroxy-4-phenyl-dibenzotropone (21) must involve a carbonium-ion type rearrangement. It is known that epoxides in the presence of protons produce carbonium ions which are capable of undergoing rearrangements. It therefore seemed of interest to investigate the acid-catalysed opening of the epoxides of methylene - and benzylidene anthrone. Depending on whether the carbonium-ion was formed on the exocyclic or endocyclic carbon atom the compounds (16) and (21) would be obtained or else the simple anthrone derivatives.

Benzylideneanthrone epoxide[33] (32) and methyleneanthrone epoxide (29) were prepared from benzylideneanthrone[29] and methyleneanthrone[31,34] respectively by treatment with alkali and hydrogen peroxide. These epoxides were first treated with concentrated sulphuric acid at 0-5° but in both the cases anthraquinone was the main product. House[35,36] has successfully used boron trifluoride-etherate in benzene solution to bring about the carbonium ion rearrangements of the epoxides of -unsaturated ketones. When methyleneanthrone epoxide was treated with boron trifluoride-etherate, a red product was immediately precipitated which was soluble in aqueous alkali. It showed strong hydrogen bonding

in the infra-red spectrum in the solid state; ie. broad absorption in 3400 cm^{-1} - 2900 cm^{-1} region and a shoulder at 1660 cm^{-1} which is consistent with a benzophenone carbonyl chromophore. The product was extremely insoluble in non-polar solvents and it was therefore impossible to decide whether the hydrogen bond was inter - or intra-molecular. If the product were 4-hydroxy-2:3-6:7-dibenzotropone (16), one would expect it to show two carbonyl peaks in the infra-red spectrum, one due to the benzophenone carbonyl and the other due to the carbonyl in the position 4. Thus it seemed that it could not be 4-hydroxy-2:3-6:7-dibenzotropone (16), but a simple derivative of anthrone.

The fact that the above product gave a mono-2:4-dinitrophenylhydrazone and also a mono-benzoate indicated a system capable of showing keto-enol tautomerism. Thus it has been assigned the structure (30), viz; 10-hydroxymethyleneanthrone which can exist as its tautomer (31).

On gentle oxidation of 10-hydroxymethyleneanthrone (30) by bubbling air through its alkaline solution at room temperature, anthraquinone and formic acid were obtained; the latter was identified by direct comparison of the infra-red spectrum of its sodium salt with an authentic sample. Because of its low solubility in methylene chloride, the ozonolysis of 10-hydroxymethyleneanthrone could not be carried out on a sufficient amount to permit the isolation of formic acid, however anthraquinone was isolated and identified. It is unlikely that such mild oxidative conditions could have caused any ring contraction.

The reduction of 10-hydroxymethyleneanthrone (30) was carried out using platinum oxide in acetic acid and, although there was an apparent uptake of hydrogen, only anthraquinone was isolated. An attempt was made to synthesise 10-hydroxymethyleneanthrone by direct formylation of anthrone

but only anthraquinone and 9-10'-bianthronyl[32] (28) were obtained.

When benzylideneanthrone epoxide (32) was treated with boron trifluoride-etherate, a product m.p.130-131° was isolated which contained all the carbon atoms of the original molecule. Its mixed melting point with Cook's compound (21) showed a marked depression. This product showed two carbonyl absorption peaks in the infra-red spectrum, one at 1715 cm^{-1} which was attributed to the carbonyl absorption of the aldehyde group while the other at 1660 cm^{-1} was attributed to the benzophenone carbonyl chromophore. This compound gave characteristic aldehydic reactions: viz, it reduced Fehling's solution and ammoniacal silver nitrate solutions. It did not dissolve in cold aqueous alkali but dissolved on heating and on acidification gave 10-hydroxy-10-phenylanthrone (34) which was identified by its mixed melting point with an authentic sample prepared by the method of Baeyer[37]. Thus the product was identified as 10-formyl-10-phenyl-anthrone (33). Oxidation of this anthrone (33) with alkaline potassium permanganate furnished 10-hydroxy-10-phenylanthrone (34). The solubility of 10-hydroxy-10-phenylanthrone in alkali was explained by assuming that it formed a transannular ion of structure (35).

From the above two reactions it was concluded that the carbonium ion formed at carbon atom No. 10 was more stable than that formed on the exocyclic carbon atom, and it was the former which took part in the reaction. Formation of the carbonium ion at carbon atom No. 10 seemed feasibl as it is both tertiary and benzylic and moreover its charge can be distributed over the two benzene rings which are in conjugation with it.

It was then decided to rearrange benzhydrilideneanthrone epoxide (37). In this case both the exocyclic and the endocyclic carbon atoms were tertiary and hence the rearrangement might be expected to go through the desired path to give 5;5-diphenyl-4-oxo-2:3-6:7-dibenzocycloheptadien-1-one (38).

Benzhydrilideneanthrone (36) was prepared by the method of Bergmann[38], but attempts to prepare the corresponding epoxide (37) both by alkali/hydrogen peroxide and pertrifluoroacetic acid treatment, failed. This observation was in keeping with that of Padova[39] who found that benzhydrilideneanthrone (36) did not react with bromine. The only explanation of these facts must be that the carbon-carbon double bond in benzhydrilideneanthrone (36) must be sterically hindered.

Having failed to form an exocyclic carbonium ion in the above two cases, the acid-catalysed rearrangement of the epoxide of 2-benzylidene-1-tetralone (39) was investigated. The epoxide (40) was prepared from 2-benzylidene-1-tetralone [40](39) by the action of alkaline hydrogen peroxide. Treatment of this epoxide with either concentrated sulphuric acid or boron trifluoride-etherate produced the same compound (41). This compound gave a negative test with ferric chloride solution. It was soluble in aqueous alkali and could be recovered unchanged on acidification. It gave a monomethyl ether with diazomethane and, on oxidative cleavage with alkaline hydrogen peroxide, both benzoic acid and β-(o-carboxylphenyl)-propionic acid[41](42) were isolated. These facts, together with an infra-red spectrum which showed maxima at 1720 cm^{-1} and 1690 cm^{-1}

and an ultra-violet absorption maximum at 295 mμ (ε=6,150) were consistent with the structure (41) assigned to this product.

Thus, in this case, the cyclohexane moiety had expanded to the cycloheptane ring, and hence, the reaction had taken a different course to that of the methylene - and benzylidene-anthrone epoxides, i.e. the carbonium ion had formed on the exocyclic carbon atom, which is benzylic in environment.

In the anthrone series, the charge on the endocyclic ion can be distributed over the two adjacent rings and hence this ring carbonium ion which is also tertiary will tend to be stabilised by these effects. On the other hand protonation of the 1-tetralone epoxide (40) will lead to formation of a carbonium ion on the benzylic carbon with concomittant acyl migration resulting in the formation of the 1:3-diketone (41).

Similar experiments have been carried out by House and his co-workers [35,36]. They have put forward a similar explanation for the formation of 2-phenyl-cycloheptane-1:3-dione. They also mentioned that they could not convert the 2-phenyl-cycloheptane-1:3-dione into its enol form whereas in the case of 2-phenyl-6:7-benzocycloheptane-1:3-dione (41), we have been able to prepare the methyl enol ether albeit in low yield. This monomethyl ether has been assigned the structure (43) because of the ultra-violet absorption maximum at 290 mμ (ε=13,043) and an infra-red maximum at 1660 cm^{-1} in nujol, which showed neither bathochromic nor hypsochromic shifts in solution.

Note: The dibromide of 2-benzylidene-1-tetralone was treated

with moist silver oxide (cf. Cook [29,30]) but the dibromide was recovered unchanged.

In an attempt to compel the formation of an exocyclic carbonium ion, we followed the work of Rigaudy and Tandieu[42] in which they have reported the rearrangement of the alcohol (44) to 2:3-6:7-dibenzotropilidene (45) by dehydration with potassium bisulphate and also by the solvolysis of the tosylate (46). The alcohol[43] (48) was prepared from the corresponding ketone[44] (47) by lithium aluminium hydride reduction. When the alcohol was dehydrated using the pyrolytic conditions of the French workers[42] the only pure product isolated was 9-benzylanthracene (49) identified by its mixed melting point with an authentic sample[29]. This aromatic hydrocarbon (49) must have been formed by dehydration of the alcohol (48) followed by aromatisation. If the reaction had taken the expected course the substituted cycloheptatriene (50) (cf. Cologne[45]) would have been obtained. Solvolysis of the tosylate of (48) in acetic acid merely brought about trans-esterification and the product isolated was the corresponding acetate.

In another attempt to prepare 4-hydroxy-2:3-6:7-dibenzo-tropone (16) and 4-hydroxy-5-phenyl-2:3-6:7-dibenzotropone (21), 2:3-6:7-dibenzotropone[46](51) was first prepared by the route shown in scheme C. 2:3-6:7-Dibenzotropone (51) was then treated with liquid bromine to form the corresponding dibromide (52) and the replacement of the bromine by acetate grouping was carried out according to the method of Treibs and Klinkhammer[27]. Hydrolysis

of the acetate then afforded the diol (54).

When a reaction was carried out between the dibromide (52) and silver acetate in glacial acetic acid which had not been vigorously dried, a diacetate m.p. ~~195°~~ 175° was obtained in addition to a mono acetate. This diacetate furnished a different diol (57) to that isolated by Treibs and Klinkhammer[27]. Pilot experiments were now carried out to elucidate this discrepancy.

1. Silver acetate was added to a suspension of the dibromide (52) in aqueous acetic acid, the reaction mixture warmed at 65° and then worked up in the usual way. The two products isolated were anthraquinone (low yield) and the corresponding cis-monoacetate (53) (the configuration of these groupings will be discussed later. See page 13). This cis-monoacetate gave the corresponding cis-diol (54) on mild hydrolysis.

2. The dibromide (52) was then treated with <u>benzh</u> acetic acid and silver acetate under the same conditions as in (1) and a mixture of the trans-diacetate (56) and the cis-monoacetate (53) (greater proportion) was isolated.

3. The dibromide (52) was treated with silver acetate and <u>anhydrous</u> acetic acid as before, and in this case, the sole product obtained was the trans-diacetate (56).

The formation of a cis-monoacetate (53) by the action of aqueous acetic acid and silver acetate from the trans-dibromide (52) and also the formation of the trans-diacetate (56) from the trans-dibromide (52) afforded added confirmation of the work of

Winstein [47]; i.e. the replacement of the bromine atom in the trans-dibromide was considered to proceed via the bromonium ion (58) which has also been postulated as an intermediate in the normal trans addition of bromine to cyclohexene[48]. The replacement of the second bromine atom then proceeded via the acetoxonium ion (59). In dry acetic acid containing excess acetate ions the final product was the trans diacetate, but in slightly aqueous acid the unstable orthomonoacetate (60) was formed. This ring structure was then opened without inversion to give the cis-monoacetate (53).

The cis-monoacetate (53) on mild hydrolysis gave a cis-diol (54) identical with one prepared by the action of osmium tetroxide on 2:3-6:7-dibenzotropone (51). (This reagent is known to bring about cis-hydroxylation of a carbon-carbon double bond). The cis-diol (54) gave the corresponding cis-diacetate (55) which was different from the diacetate (56) prepared by acetylation of the trans dibromide (52). Hydrolysis of this trans diacetate (56) furnished the corresponding trans diol (57). Both the cis-diol (54) and the trans-diol (57) retained their configuration on refluxing with acetic acid.

Both these diols (54, 57) gave a colourless solution in aqueous alkali and were recovered on acidification with their respective configurations retained. Treibs[27] had explained this solubility in alkali by assuming that the diols formed an o-quinonoid structure (61).

An alternative explanation may be found in the formation of

the corresponding hemiacetal structure (62) since the alkaline solution of either diol was colourless and the corresponding diols could be recovered by acidification with no inversion. In addition, on methylation, the two diols furnished two different mono-methylated products: (63, 64) (cf: o-quinonoid form).

A comparison of the ultra-violet spectra of the compounds listed below seem to exclude the possibility of conjugation of o-quinonoid type. A similar type of structure has been advanced both by Mignudy and Nedelec [49] to explain the solubility of the hydroxy-1:2-dione (66) in alkali and by Schmitz [50] in connection with the solubility of the o-phthaldehyde in alkali.

No.	Compound	Solvent	max.	Extinction
1.	4:5-Dihydroxy-2:3-6:7 dibenzocycloheptadiene-1-one	alcohol	270	10,390
2.	2:3-6:7-Dibenzocyclohepta-diene-1-one	alcohol	270	31,000
3.	4:5-Dihydroxy-2:3-6:7-dibenzocycloheptadiene	sodium hydroxide solution (10%)	268	925
4.	4-Hydroxy-1-methoxy-1:5-oxide-2:3-6:7-dibenzo-cycloheptadiene	alcohol	268	724
5.	2:3-6:7-Dibenzocyclohepta-diene	alcohol	266	709

Oxidation of both the monomethyl ethers (63,64) produced the same ketone (65). This ketone (65) was then treated with phenyl lithium to furnish the hemiacetal methyl ether of 4:5-hydroxy-4-

phenyl-2:3-6:7-dibenzocycloheptane-1-one (68). This compound (68) was the potential source of 5-hydroxy-4-phenyl-2:3-6:7-dibenzotropone (2 However when attempts to open the hemiketal ring were carried out, the only product isolated proved to be 10-phenylanthrone[51] (70) i.e. formation of the diol (69) resulted in a pinacol-pinacolone rearrangement with contraction of the seven-membered ring into the corresponding six-membered one. The initial product therefore was 10-formyl-10-phenylanthrone (33) which was unstable in the acid medium and reacted further as a vinylogous 1:3-dicarbonyl system to furnish 10-phenylanthrone (70).

Attempts to prepare 4-hydroxy-2:3-6:7-dibenzotropone (16) by dehydration of either diol (54, 57) likewise resulted in the formation of 10-hydroxymethyleneanthrone (30). The substituted 4-hydroxy-tropone (16) might have been prepared by the pyrolytic elimination of acetic acid from the trans-diacetate (56) but under a variety of conditions, trans-diacetate remained unchanged or else furnished anthraquinone.

While this work was in progress Rigaudy and Nedelec[52] reported the synthesis of 4-hydroxy-2:3-6:7-dibenzotropone (16) and their route is shown in scheme D. Their synthesis started from o-benzylbenzoic acid (71) and prepared its homologous acid (72) which on cyclisation gave 4-oxo-2:3-6:7-dibenzocycloheptane (73). The ketone (73) on treatment with selenium dioxide furnished the triketone (74). Wolff-Kishner reduction of the mono-hydrazone of the triketone (74) furnished the required 4-hydroxy-2:3-6:7-dibenzotropone (16). It dissolved in alkali with a red colour and gave a mono-benzoate

and a mono-2:4-dinitrophenylhydrazone. The above properties confirm that the 4-hydroxytropone (16) could exist in its tautomeric form (16A), (cf. Cook[29,30]). 4-Hydroxy-2:3-6:7-dibenzotropone is stable at room temperature in absence of air, but readily changes to its ketone tautomer (16A) on heating.

It was evident at this point, that Cook's ring expansion method was not of general interest, and that the other obvious routes were limited in their application. The work was therefore abandoned.

EXPERIMENTAL

Anthrone (18) was prepared according to the method of Meyer.[53,54]

A mixture of anthraquinone (50g.), glacial acetic acid (375 ml.) and granulated tin (50g.) was heated to boiling, and concentrated hydrochloric acid (125 ml.) then added over a period of two hours to this boiling solution. When all the anthraquinone and tin had dissolved, the solution was filtered, water (50 ml.) added, and anthrone separated out as a yellowish-white precipitate which crystallised from benzene/petroleum ether (60-80°) as long needles (35-40g., 75-80%) m.p. 154-155° (lit. m.p., 154-155°).

Methyleneanthrone (26): was prepared by the method of Barnett[55].

A mixture of anthrone (20g.), absolute ethanol (200 ml.) and formalin solution (25 ml., 40%) was heated to boiling and a few drops of piperidine were then added. The solution gradually turned orange in colour and was refluxed for one hour. On cooling to room temperature long yellow needles of methyleneanthrone separated out. This crop was collected, washed with ethanol, water and dried (11g. 55%) m.p. 142-144° (lit. m.p., 148°).

Methyleneanthrone dibromide (27).

A suspension of methleneanthrone (18.9g.) in acetic acid (50 ml.) was treated with a solution of bromine in acetic acid (92.5 ml., 8%). A cold water bath was used to cool the reaction mixture. When this addition was complete, the solution turned pale red and the white dibromide separated out. The reaction mixture was allowed to stand at room temperature for a further fifteen minutes before filtration.

The crude dibromide was washed with acetic acid, water, dried, and recrystallised from benzene or petroleum ether (60-80°) in needles (27g, 84%) m.p. 140° (lit.[31] m.p. 135-140°).

Attempted rearrangement of methyleneanthrone dibromide (27) with moist silver oxide:

To a solution of methyleneanthrone dibromide (15g.) in acetone (150 ml.) and water (20 ml.), freshly precipitated silver hydroxide (10g.) was added with shaking. A further amount of silver hydroxide (2g.) was then added and the black reaction mixture shaken for two hours and thirty minutes, followed by reflux for thirty minutes. The cooled reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The solid residue crystallised from dioxan to furnish 10-10'-bianthronyl (6g., 43%) as needles m.p. 260° (decomp.). This sample showed no depression of melting point on admixture with an authentic sample.[32]

Methyleneanthrone epoxide (29):

A solution of methyleneanthrone (1g.) in ethanol (10 ml.) was treated with aqueous sodium hydroxide solution (2 ml., 10%) and hydrogen peroxide (2 ml., 15%). This yellow reaction mixture was warmed on a steam bath for two to three minutes, when the colour of the solution changed from yellow to green, and finally to red. After cooling to room temperature for one hour methyleneanthrone epoxide separated out. The crude epoxide was collected, washed with alcohol, water and dried, (.7g, 63%). It was crystallised from ethanol in needles m.p. 126-129°

Found C, 81.1; H, 4.7; $C_{15}H_{10}O_2$ requires C, 81.1, H, 4.5%.

10-hydroxymethyleneanthrone (30):

A solution of methyleneanthrone epoxide (1g.) in benzene (15 ml.) was treated with boron trifluoride-etherate (1 ml.) and the red crystalline solid which precipitated was filtered off, washed with benzene, and dried. Attempts to crystallise this compound always resulted in the production of a mixture of 10-hydroxymethyleneanthrone and anthraquinone. The best method of purification was by precipitation with mineral acid of the compound from its solution in aqueous alkali. The pure product (c.8g, 80%) thus obtained had m.p. 185-187°. It was insoluble in benzene, petroleum ether and chloroform. The infra-red spectrum, (nujol mull), showed broad absorption between 3400 cm^{-1} and 2500 cm^{-1} indicative of strong hydrogen bonding.

The corresponding mono-2:4-dinitrophenylhydrazone crystallised from acetic acid in dark green needles m.p. 300°; Found N, 13.95.

$C_{21}H_{14}N_4O_5$ requires N, 13.95%.

The corresponding benzoate, formed by the normal Schotten-Baumann method, was crystallised from ethanol in colourless needles, m.p. 165-166°. Found; C, 80-75, H, 4.3; $C_{22}H_{14}O_3$ requires C, 80.5; H, 4.35%.

Attempted Synthesis of 10-hydroxymethlene anthrone (30):

A stirred suspension of solid sodium ethoxide (prepared from sodium (c.44g.), and dry ethanol (20 ml.) in anhydrous benzene (10 ml.) was placed in a nitrogen atmosphere while being treated successively with anthrone (1.98g.) and ethyl formate (1.6 ml.). After stirring overnight at room temperature, the black reaction mixture was diluted with water and extracted with ether. The ethereal solution was dried

and the solvent removed to furnish a yellow solid which crystallised from benzene as yellow needles (0.23g.) m.p. 276°. This product was identical in all respects with an authentic specimen of anthraquinone. The aqueous layer from the above extraction still contained solid material which was insoluble in cold benzene or ether. This yellow solid was collected, dried and recrystallised from alcohol in pale yellow needles m.p. 240-245°. This product showed no depression in melting point when mixed with an authentic sample of 10-10'-bianthronyl[32].

Attempted reduction of 10-hydroxymethyleneanthrone (30):

A catalytic reduction of 10-hydroxymethyleneanthrone using platinum oxide and glacial acetic acid furnished anthraquinone as the sole product.

Oxidation of 10-hydroxymethyleneanthrone (30):

Air was bubbled through a solution of 10-hydroxymethyleneanthrone (1.0g.) in aqueous sodium hydroxide solution for fifty hours. The crude anthraquinone so precipitated was collected and recrystallised (0.45g., 50%) as before m.p. 278-280°.

The alkaline filtrate was acidified with concentrated hydrochloric acid and distilled. The distillate was neutralised with an aqueous sodium hydroxide solution (phenolphthalein as the indicator) and then evaporated to dryness. The infra-red spectrum of the residue which contained sodium formate, and a little sodium chloride and sodium hydroxide, was identical with that of an authentic specimen of sodium formate.

Ozonolysis of 10-hydroxymethyleneanthrone (30):

Ozone was passed through a solution of 10-hydroxymethyleneanthrone

(0.100g.) in distilled methylene chloride (200 ml.) at 0-5° for fifteen minutes. Water (1 ml.) was then added and solution heated for ten minutes. Methylene chloride was then removed under reduced pressure and the residue was crystallised from benzene to give anthraquinone as yellow needles m.p. 278-280°. This sample was identical in all respects with an authentic sample.

Benzylideneanthrone (19): was prepared by the method described by Cook[29].

Benzylideneanthrone epoxide (32):

Aqueous sodium hydroxide solution (4 ml., 10%) and hydrogen peroxide (4 ml., 15%) were added to a solution of benzylideneanthrone (2g.) in ethanol (40 ml.). The reaction mixture was warmed on the steam bath for a few minutes and then allowed to stand at room temperature for one hour. At the end of this time, the precipitated epoxide was collected, washed with water and rectified spirits, and then recrystallised from ethanol in yellow cubes (1.13g., 55%) m.p. 130-131° (Weitz[33] recorded m.p. 133°).

Treatment of Benzylideneanthrone epoxide (32) with concentrated sulphuric acid:

Ice-cold concentrated sulphuric acid (10 ml.) was added to benzylideneanthrone epoxide (1g.) and the resultant dark red solution held at 0° for one hour. The reaction mixture was then poured on to ice-water and the yellow precipitate collected, washed with water and dried. When this material was refluxed in ethanol a little solid remained undissolved. This was collected and found to be anthraquinone and from the cooled alcoholic solution benzylidene-anthrone crystallised as yellow needles m.p. 115-117°.

10-Formyl-10-phenylanthrone (33):

Boron trifluoride-etherate (2.15 ml.) was added to a solution of benzylideneanthrone epoxide (2.98g.) in benzene (30 ml.) and the dark red reaction mixture allowed to stand at room temperature for ten minutes before dilution with ether. The ethereal layer was washed with water and dried over anhydrous magnesium sulphate, filtered and concentrated to approximately 5 ml. The yellow crystalline solid which was deposited on cooling was filtered off and recrystallised from ethanol to furnish 10-formyl-10-phenylanthrone (33) in yellow needles (1.4g., 47%) m.p. 130-131°. Found; C, 84.8; H, 4.85 $C_{22}H_{14}O_2$ requires C, 84.55, H, 4.75%.

When 10-formyl-10-phenylanthrone was dissolved in hot aqueous sodium hydroxide solution, cooled and then treated with aqueous mineral acid, the compound so precipitated was collected and recrystallised from benzene petroleum ether (60-80°) as a micro-crystalline powder, m.p. 214-215°. This was shown to be 10-hydroxy-10-phenylanthrone (34) by comparison with an authentic sample [37].

10-Formyl-10-phenylanthrone gave the characteristic reactions of an aldehyde, i.e. it reduced ammoniacal silver nitrate solution, Fehling's solution and decolourised alkaline potassium permanganate solution; the infra-red spectrum in nujol showed maxima at 1715 cm^{-1} and 1660 cm^{-1}.

10-Hydroxy-10-phenylanthrone (34):

An excess of saturated potassium permanganate solution (22 ml.) was added to a solution of the 10-formyl-10-phenylanthrone (0.2) obtained above in aqueous sodium hydroxide solution (10 ml., 8%). Sulphuric acid was then added followed by aqueous sodium bisulphite

solution until the reaction mixture became colourless. The reaction mixture was thoroughly extracted with ether. The ethereal extracts were washed with water, dried, the solvent removed and the residue was crystallised from benzene/petroleum ether (60-80°) as a microcrystalline solid (0.06g., 32%) m.p. 214-215°. This melting point was undepressed on admixture with an authentic sample[37]. The infra-red spectra of the two samples were superposable.

Benzhydrylideneanthrone (36): was prepared by the method of Padova[56] from anthrone and dichloro-diphenylmethane.

Attempted preparation of Benzhydrylideneanthrone epoxide (37):

(a). Aqueous sodium hydroxide solution (2 ml., 10%) and hydrogen peroxide (2 ml., 15%) were added to a solution of benzhydrylideneanthrone (1g.). The reaction mixture was heated on the steam bath for two to three minutes. From standard work up of the reaction mixture benzhydrylideneanthrone was recovered unchanged.

(b). On extending the reflux period of the above reaction to three hours, there was still no epoxide formed.

(c). Trifluoroacetic anhydride (1.8 ml.) was added to a stirred suspension of hydrogen peroxide (0.3 ml., 90%) in methylene chloride (2.5 ml.), cooled in an ice bath. The resulting solution was stirred for ten minutes in cold. It was then added dropwise to a solution of benzyhdrylideneanthrone (1.52g.) and triethylammonium acetate (1.0g.) in methylene chloride (10 ml.). The whole reaction mixture was then stirred at room temperature for thirty minutes and on removal of the solvents, benzhydrylideneanthrone was recovered unchanged.

2-Benzylidene- 1-tetralone (39): was prepared according to the method of Kapson[40] and found to crystallise from ethanol in cubes m.p. 107° (lit. value m.p. 105°). Its infra-red spectrum (nujol mull) showed absorption peaks at, 1665 cm^{-1}, 1610 cm^{-1}, 1600 cm^{-1}.

2-Benzylidene- 1-tetralone epoxide (40):

An aqueous sodium hydroxide solution (12 ml., 8%) and hydrogen peroxide (12 ml., 15%) were added to a solution of 2-benzylidene- 1-tetralone (5g.) in ethanol (60 ml.), the reaction mixture warmed on a steam bath for a few minutes, and then allowed to stand at room temperature for sixteen hours. The reaction mixture was then poured into water and thoroughly extracted with ether. The combined ethereal extracts were washed with water, dried and the solvent removed to furnish a solid which recrystallised from ethanol to give 2-benzylidene- 1-tetralone epoxide (5.1g., 78%) in cubes, m.p. 107° (lit[58] m.p. 77° - 77.5°). Found; C, 81.9; H, 5.55; $C_{17}H_{14}O_2$ requires C, 81.6; H, 5.55%. Its infra-red spectrum (nujol mull) showed absorption peaks at 1700 cm^{-1}. 1603 cm^{-1}.

2- Benzylidene- 1-tetralone dibromide (39A):

Bromine (0.43 ml.)was added to a solution of 2-benzylidene- 1-tetralone (2g.) in carbon disulphide (15 ml.) and left at room temperature overnight. The reaction mixture was then evaporated to dryness and the residual solid recrystallised from ethanol in stout prisms (2g. 68%) m.p. 113°, (lit.[58] m.p. 153-154°; 118-119°.).

Action of moist silver oxide on 2-benzylidene- 1-tetralone dibromide (39A):

Freshly precipitated silver hydroxide (1.9g.) was added to a solution of the dibromide (1.24g.) in aqueous acetone (30 ml., 75%)

the reaction mixture heated to reflux and then allowed to stand at room temperature for three hours. The filtered reaction mixture was concentrated and the dibromide crystallised out unchanged.

A repeat reaction was carried out with an extended reflux period (43 hours) but once again no reaction took place.

2-Phenyl-4:5-benzocyclohepten-1:3-dione (41):

a) 2-Benzylidene- 1-tetralone epoxide (1g.) was treated with concentrated sulphuric acid (10 ml.) at 0.5° for one hour and then poured onto crushed ice. The resultant solid was collected, washed with water, dried and recrystallised from petroleum-ether (40-60) to furnish 2-phenyl-4:5-benzocyclohepten-1:3-dione as needles (0.9g., 90%) m.p. 86-87°. Found: C,81.8; H,5.85; $C_{17}H_{14}O_2$ requires C, 81.6; H, 5.65%. This compound dissolved in sodium hydroxide solution and could be recovered unchanged on acidification. It did not give a colour test with a ferric chloride solution. It also decolourised alkaline potassium permanganate solution.

The infra-red spectrum (nujol mull) showed no absorption in the hydroxyl region but two peaks at 1720 cm^{-1} and 1690 cm^{-1} indicative of the structure (41) rather than the enol form. The ultra violet absorption spectrum had maximum at 295 mμ (ε = 6,150).

b) A solution of the epoxide (0.3g.) had boron trifluoride-ethereate (0.6 ml.) in dry benzene (7 ml.) was allowed to stand at room temperature for fifteen minutes, then diluted with ether and washed with water. The organic layer was then dried over in magnesium sulphate, filtered and the solvent removed under reduced pressure. The residual gum was dissolved in petroleum-ether (40-60°) and 2-phenyl-4:5-benzocyclohepten-1:3-dione (0.1g., 33%) crystallised

out in needles m.p. 85-86°. This sample was identical in all respects with the sample prepared above.

3-Methoxy-2-phenyl-4:5-benzocyclohepta-2:4-diene-1-one.(43):

An ethereal solution of diazomethane was added in slight excess to a solution of the diketone (41: 1g.) in anhydrous ether and the reaction mixture allowed to stand for two days. The reaction mixture was then washed with dilute aqueous sodium hydroxide solution, water and dried. Removal of the solvent furnished the crude enol ether which recrystallised from methanol in colourless plates (0.5g., 48%) m.p. 84-86°. Found: C, 82.0; H, 6.15,; $C_{18}H_{16}O_2$ requires C, 81.8; H, 6.1%. The infra-red absorption spectrum both in nujol and solution showed one peak at 1660$^{cm^{-1}}$. Its ultra-violet spectrum in ethanol had the absorption maximum at 290 mμ (ε=13,043).

Oxidative cleavage of 2-phenyl-4:5-benzocyclohepten-1:3-dione (41).

Hydrogen peroxide (2 ml.; 30%) was added to a solution of the diketone (0.1g.) in aqueous sodium hydroxide solution and the reaction mixture then allowed to stand at room temperature for seventeen hours. The reaction mixture was acidified with concentrated hydrochloric acid and then thoroughly extracted with ether. The combined ethereal extracts were washed with water, dried and the solvent removed to give a solid residue. Sublimation of this residue resulted in the isolation of benzoic acid (0.01g.) m.p. 120-121° identical in all respects with an authentic sample. The residue from this sublimation crystallised from water in needles (0.04g.) m.p. 168°. This material was identified as β-(O-carboxyphenyl) propionic acid by comparison with an authentic sample.[41]

10-Benzoyl-9:10-dihydroanthracene (47): was prepared according to the method of Cook.[44]

10-(α-Hydroxybenzyl)-9:10-dihydroanthracene (48):

To a solution of 10-benzoyl-9:10-dihydroanthracene in anhydrous ether (130 ml.) which was kept under nitrogen atmosphere, an excess of lithium-aluminium hydride (0.5g.) was added and the reaction mixture stirred for three hours at room temperature. It was then added to a mixture of ice and dilute sulphuric acid (12 ml., 10%) and the ether layer separated. The ether solution washed with saturated sodium bicarbonate solution, water, dried and the solution evaporated to dryness. The solid residue thus obtained was crystallised from ethanol as needles, (0.90g.90%) m.p. 150° (lit.[43] m.p. 156-157°). Its infra-red spectrum (nujol mull) showed hydroxyl absorption at 3450 cm^{-1}.

It gave a para-toluene sulphonate m.p. 96-97°.

Attempted dehydration of the 10-(α-hydroxybenzyl) 9:10-dihydro-anthracene (48):

A finely ground mixture of the alcohol (48, 1.0g.) and fused potassium bisulphate (0.7g.) was heated at 220-230° for fifteen minutes. To this fused mass water was added and the insoluble organic material was collected. On chromatography of this material on alumina, 9-benzylanthracene (0.21g., 29%) was eluted with petroleum ether (60-80°). It crystallised from alcohol m.p. 133-134°. The melting point on admixture with an authentic specimen prepared by the method of Cook[29] was not lowered.

On further elution of the alumina with a mixture of benzene-petroleum ether (50%) another product (0.2g.) was obtained which could not be crystallised to a definite melting point.

Solvolysis of the tosylate of 10-(α-hydroxybenzy) 9:10-dihydro-anthracene (48):

A solution of the tosylate (0.5g.) in glacial acid (5.0 ml.) was refluxed for thirty minutes and then left for another sixteen hours at room temperature when white needles were obtained. This material was collected and crystallised from ethanol to furnish the acetate of the alcohol (48) as needles (0.30g.,81.0%) m.p. 156°: Found: C,84.25: H,6.25: $C_{23}H_{20}O_2$ requires C,84.1%;H,6.15%.

2:3-6:7-Dibenzotropone (51) was prepared according to the method of Cope and Fenton [46].

4:5-Dibromo-2:3-6:7-dibenzocycloheptadien-1-one (52):

Bromine (0.51 ml.) was added dropwise to a solution of 2:3-6:7-dibenzotropone (1.3g.) in glacial acetate acid held at room temperature. The dibromide immediately started to crystallise out of the reaction mixture. The solution was allowed to stand for fifteen minutes and then filtered and the crude dibromide washed with methanol and dried (2.0g., 87%) m.p. 210°(lit.[27] m.p.211°.

Cis-4:5-dihydroxy-2:3-6:7-dibenzocycloheptadien-1-one (54):

A solution of 2:3-6:7-dibenzotropone (0.3g.) in dry benzene(2.5 ml.) was treated with a solution of osmium tetroxide (0.38g.) in dry benzene (2 ml.). Pyridine (0.22 ml.) was then added, and the raction mixture allowed to stand at room temperature for six days. The black complex which precipitated was filtered off, suspended in ethanol (32 ml.) and treated with an aqueous solution of sodium sulphate (7g in water 16 ml.)

This reaction mixture was refluxed for thirty minutes, filtered and the black residue re-extracted with boiling ethanol. The combined

combined alcoholic solutions were concentrated and yielded, on cooling, Cis-4:5-dihydroxy-2:3-6:7 dibenzocycloheptadien-1-one which recrystallised from benzene in needles (0.1g.,28%) m.p. 130-131°. Its infra-red absorption spectrum (nujol mull), showed a hydroxyl peak at 3380 cm^{-1} and the carbonyl absorption peak at 1633 cm^{-1}.

Treatment of 4:5-dibromo-2:3-6:7-dibenzocycloheptadien-1-one (52) with silver acetate and acetic acid.

a) Silver acetate (1g) was added to a suspension of the dibromide (1g.) in aqueous acetic acid (90%) and the reaction stirred at 60-65° for four hours. The cooled reaction mixture was filtered and the filtrate poured into water. The yellow solid which precipitated at this stage was collected (0.14g.) and identified as anthraquinone. The above filtrate was then thoroughly extracted with saturated sodium bicarbonate solution, water and dried over magnesium sulphate. Removal of the solvent under reduced pressure furnished the monoacetate of cis-4:5-dihydroxy-2:3-6:7-dibenzocycloheptadien-1-one as a thick gum.

The infra-red spectrum, in nujol, showed characteristic maxima at 3400 cm^{-1} (-OH grouping); 1735 cm^{-1} (-O-COCH_3 grouping) and 1660 cm^{-1} (benzophenone carbonyl).

b) Dry silver acetate (2g) was added to a suspension of the above di-bromide (2g) in bench "glacial" acetic acid (80 ml.) and the reaction mixture stirred at 60-65° for four hours. The cooled solution was filtered free of silver bromide and then diluted with water. A small amount (0.1g.) of trans-4:5-diacetoxy-2:3-6:7-dibenzocyclohep/

dibenzocycloheptadien-1-one (56) crystallised out in long needles. This material was filtered off andthe filtrate thoroughly extracted with ether. The ethereal extracts were washed with saturated sodium bicarbonate solution, water, dried and the solvent removed under reduced pressure to furnish the cis monoacetate (53) as a gum (1.4g).

c) Acetic acid (120 ml.) was refluxed with acetic anhydride (12 ml.) for three hours, the mixture distilled and the fraction boiling at 118° was collected and used as anhydrous acetic acid.

Dry silver acetate (1g.) was added to a suspension of the dibromide (1g.) in anhydrous acetic acid (40 ml.) and the mixture stirred at 60-65° for four hours. The cooled reaction mixture was filtered and the filtrate diluted with water. The white precipitate so formed was collected, dried and recrystallised from ethanol to furnish trans-4:5-diacetoxy-2:3-6:7-dibenzocycloheptadien-1-one (56) as elongated needles (0.7g.,77%) m.p.196°. Found: C,70.4; H,5.0; $C_{19}H_{16}O_5$ requires C,70.35; H,5.0%. The infra-red spectrum (in nujol) exhibited maxima at 1743 cm^{-1} (-O-$COCH_3$ grouping) and 1660 cm^{-1} (benzophenone carbonyl). There was no indication of an absorption peak in 3,400 cm^{-1} (-OH) region.

Cis-4:5-dihydroxy-2:3-6:7-dibenzocycloheptadien-1-one (54):

Dry silver acetate (2g) was added to a suspension of the dibromide (53) in bench "glacial" acetic acid (80 ml.) and the reaction mixture heated at 60-65° for four hours. After removal of the silver bromide, the reaction mixture was diluted with water, separated from any small amount of trans-diacetate (56) and thoroughly extracted with ether. The ethereal extracts were washed with saturated sodium bicarbonate solution, water,

dried and the solvent removed under reduced pressure. The residual glassy cis-monoacetate (53) was dissolved in methanol (20 ml.) and refluxed with potassium hydroxide (1.2g.) solid dissolved in water and acidified with concentrated hydrochloric acid. Ether extraction followed by washing of the ethereal extracts with water, drying over magnesium sulphate and removal of the solvent, furnished cis-4:5-dihydroxy-2:3-6:7-dibenzocycloheptadien-1-one (54) which crystallised from benzene-petroleum ether (60-80°) in cubes (0.55g. 52%), m.p. 130-131° undepressed on admixture with an authentic sample prepared above. The infra-red spectrum (nujol mull) was identical with the authentic sample. This diol dissolved to give a colourless solution in aqueous alkali and could be recovered unchanged on acidification. The ultra-violet absorption spectrum showed a maximum at 270 mμ (ε=10,390), and in alkali (10%) max at 270 mμ (ε=925).

Cis-4:5-diacetoxy-2:3-6:7-dibenzocycloheptadien-1-one (55).

A solution of the cis-diol, (54, 0.2g.) in acetic anhydride (0.37 ml.) was refluxed for three hours, then cooled and poured into ice-water (5 ml.) The crude cis-diacetate which precipitated out was filtered off, dried and recrystallised from ethanol in needles to furnish pure cis-4:5-diacetoxy-2:3-6:7-dibenzocycloheptadien-1-one, (0.19g.) 73%, m.p.156°. Found; C,70.4°; H,5.48. $C_{19}H_{16}O_5$ requires C,70.4; H,5%. A mixed melting point with the trans-diacetate (56) showed a marked depression. The cis-diacetate (55) was also prepared from the cis-monoacetate (53) by similar reaction conditions.

Trans-4:5-dihydroxy-2:3-6:7-dibenzocycloheptadien-1-one (57).

Trans-4:5-diacetoxy-2:3-6:7-dibenzocycloheptadien-1-one (1g.) was refluxed with a solution of potassium hydroxide (1.5g.) in methanol (100 ml.) for fifteen minutes. The reaction mixture was then evaporated to dryness

under reduced pressure, the solid residue dissolved in water and acidified with concentrated hydrochloric acid. Ether extraction followed by washing the etherial solution with water, drying and removal of the solvent furnished the trans-diol (57) which recrystallised from benzene-petroleum ether (60-80°) in needles (0.5g.90%)m.p. 155-156°; Found: C,75.0; H,5.5; $C_{15}H_{12}O_3$ requires C,75.0; H,5.05%. Its infra-red absorption spectrum (nujol mull) showed two hydroxyl peaks at 3349 cm^{-1}, 3380 cm^{-1} and carbonyl absorption peak at 1643 cm^{-1}.

This compound showed a marked depression in melting point when mixed with the Cis-diol.(54). As in the case of the Cis-diol, the trans-diol could be recovered unchanged from acidification of its colourless solution in alkali

Acetonide of Cis-4:5-dihydroxy-2:3-6:7-Dibenzocycloheptadien-1-one.(54A).

A mixture of the cis-diol (54, 0.44g) acetone (8 ml.) and concentrated sulphuric acid (0.32 ml.) was shaken at room temperature for six hours. Solid sodium carbonate was then added to neutralise the mineral acid, the reaction mixture filtered and the filtrate evaporated to dryness at room temperature. The residual solid was recrystallised from petroleum ether (60-80°) to furnish the acetonide of the Cis-diol in plates, (0.2g, 23%) m.p.151-153°. Found: C,77.45; H.5.85; $C_{18}H_{16}O_3$ requires C,77.1; H.5.75%.

The acetonide of trans - 4:5-dihydroxy-2:3-6:7-dibenzocycloheptadien-1-one was prepared in a similar manner and recrystallised from ethanol in needles m.p.99-100°. Found; C.77.85; H,5.95. $C_{18}H_{16}O_3$ requires C,77.1; H,5.75%.

Oxidative cleavage of Cis-4:5-dihydroxy-2:3-6:7-dibenzocycloheptadien-1-one.

A solution of sodium metaperiodate (0.24g.) in water (4.5 ml) was added to the Cis-diol (0.11g.) dissolved in ethanol (4 ml.), the mixture warmed to obtain a clear solution and then left at room temperature overnight. The filtered reaction mixture was evaporated to dryness under reduced pressure and the residual gum (0.05g;50%) when dissolved in petroleum-ether (60-80°) 2-2'-diformylbenzophenone crystallised from this solution in needles m.p.118-119°. Found C.75.05, H,4.4. $C_{15}H_{10}O_3$ requires C,75.6; H.4.25%. The infra-red spectrum (nujol mull) exhibited maxima at 1680 cm^{-1} (Aromatic Aldehyde) and 1660 cm^{-1} (benzophenone carbonyl). There was no peak at 2700-2500 cm^{-1} normally associated with the CH frequency of an aldehyde grouping.

When the trans-diol (57) was treated in the above manner, 2-2 diformylbenzophenone was again isolated.

4-Hydroxy-1-Methoxy-1:5-oxido-2:3-6:7-dibenzocycloheptadien. (63).

A mixture of dimethyl sulphate (1.2 ml.) and the Cis-diol (0.12g) dissolved in aqueous sodium hydroxide (4.5 ml.,10%) was stirred for thirty minutes and then thoroughly extracted with ether. The ethereal extract was washed with water, dried and the solvent removed. The solid residue recrystallised from petroleum-ether (40-60°) to furnish the required hemi-ketal methyl ether as needles (0.06g; 50%) m.p.134°. Found;C,75.75; H,5.9. $C_{16}H_{14}O_3$ requires C,75.55; H.5.55%. Its ultra-violet absorption spectrum showed a maximum at 268 mμ (ε =726).

When the corresponding hemi-ketal (64) was prepared in a similar manner from the trans-diol,it was found to recrystallise from petroleum-ether (60-80°) in cubes m.p.214-215°. Found; C,75.15; H,5.55. $C_{16}H_{14}O_3$ requires C,75.55; H,5.55%.

1-Methoxy-1:5-Oxido-2:3-6:7-dibenzocycloheptadien-4-one (65).

A solution of the cis hemi-ketalmethyl ether (63) (0.056 g.) in dry pyridine (0.5 ml.) was treated with a solution of chromium trioxide (0.063g.) in dry pyridine (0.6 ml.) and allowed to stand at room temperature for seventeen hours. The reaction mixture was then poured into ice-water, and thoroughly extracted with ether. The combined ethereal extracts were washed with water, dried and evaporated to dryness under reduced pressure. The solid residue crystallised from alcohol to give the keto-hemiketalmethyl ether (65) as cubes (0.04g, 70%) m.p.136-137°. Found; C,70.2; H,4.7%. $C_{16}H_{12}O_3$ requires C,76.2, H,4.8%. The infra-red spectrum (in carbon tetrachloride solution) showed no hydroxyl absorption, and one maxima at 1713 cm^{-1} (cycloheptenone).

The same keto-hemi-ketal was obtained when the corresponding trans-hemiketal-methyl ether (64) was oxidised in the above manner.

4-Phenyl-4-Hydroxy-1-methoxy-1:5-oxido-2:3-6:7-dibenzocycloheptadien (68).

An ethereal solution of phenyllithum was prepared and standardised according to the literature [57] method.

A stirred solution of the keto-hemiketalmethyl ether (65.0. 18g.) in dry ether (10 ml.) was treated under an atmosphere of nitrogen, with an ethereal phenyllithium (1.25 ml. of a solution containing 0.109g. of phenyllithium) solution and then refluxed for thirty minutes. The reaction mixture was poured onto crushed ice and extracted with ether. The combined ethereal extracts were washed with water, dried over magnesium sulphate, filtered and the solvent removed. The residual solid was crystallised from petroleum ether (60-80°) to furnish the

phenyl carbinol (68, 0.19 g.82%) in needles m.p.177-178°. Found; C,79.8; H,5.35. $C_{22}H_{18}O_3$ requires C,80.0; H,5.5%. The infra-red spectrum (in carbon tetrachloride solution) showed no carbonyl absorption, but a strong maxima at 3540 cm^{-1} (tertiary - OH).

Attempted preparation of 4:5-dihydroxy-4-phenyl-2:3-6:7-dibenzo-cycloheptadien-1-one (21).

A variety of reaction conditions were used in an attempt to open the hemiketalmethyl ether (68).

1). A solution of the hemiketalmethyl ether (68,0.52g) in acetic acid (10 ml.) and dilute sulphuric acid (10 ml.) was refluxed for fortyfive minutes and then concentrated under reduced pressure, to approximately 10 ml. The yellow precipitate so obtained was collected, dried and recrystallised from alcohol in needles (0.010g.55%) m.p. 139-140°. It was identified as 10-phenylanthrone by its mixed melting point with an authentic sample.[51]

2). The hemiketalmethyl ether (0.100 g.) was unaffected by treatment with methanolic sulphuric acid either in the cold or after thirty minutes reflux.

3). Treatment of a solution of the hemiketalmethyl ether in benzene with dry hydrogen chloride gas was equally ineffective.

Attempted hydrogenolysis of 4-phenyl-4-hydroxy-1-methoxy-1:5-oxido-2:3-6:7-dibenzocycloheptadiene (68).

a) A solution of the hemiketalmethyl ether (68, 0.3g.) in acetic acid was hydrogenated using 5% Palladium/charcoal under 4 atmospheres of hydrogen at 65°, for four hours, but after the normal work-up, starting material was recovered unchanged.

b) A solution of the hemiketalmethyl ether (68; 0.135g) in acetic acid was hydrogenated at 100° under 4 atmospheres of hydrogen for three hours using reduced platinum oxide, but here again starting material was recovered unchanged.

Attempted dehydration of cis-4:5-dihydroxy-2:3-6:7-dibenzocycloheptadien-1-one.(54).

Concentrated sulphuric acid (1ml) chilled to 0° was added to the cis-diol (0.2g.) and the reaction mixture stirred for a few minutes before being poured onto crushed ice. Ether extraction followed by washing of the ethereal layer with water, drying and removal of the solvent furnished 10-hydroxymethylene anthrone (0.06g. 31%) which crystallised from benzene as needles m.p.184-185°. The infra-red spectrum of this sample was identical to that of an authentic sample of 10-hydroxymethylene anthrone. (see previous work).

10-Hydroxymethylene anthrone was also obtained when trans-4:5-dihydroxy-2:3-6:7- dibenzocycloheptadien-1-one was treated with concentrated sulphuric acid as above.

Attempted pyrolysis of trans-4:5-diacetoxy-2:3-6:7-dibenzocycloheptadien-1-one.(56).

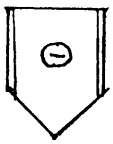
a)The trans diacetate (0.1g.) was heated at 180-220°under reduced pressure (2 m.m.) but the starting material simply sublimed out unchanged.

b) The trans diacetate (0.1g.) was heated at 220°but here again no reaction was detected and the starting material was recovered.

c) Heating the trans-diacetate (0.1g.) in a sealed tube at 220-240° was equally unsuccessful.

d) The trans-diacetate (0.3g.) was heated in triethylene glycol for

fortyfive minutes, then cooled and poured into water. A yellow solid was precipitated which was collected and identified as anthraquinone (0.1g.) m.p.280° since it showed no depression of melting point on admixture with an authentic sample.



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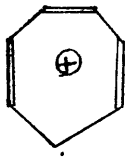

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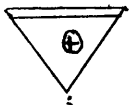

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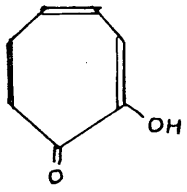

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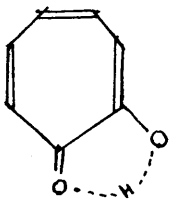

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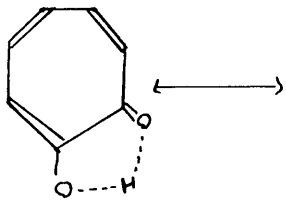

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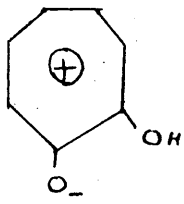

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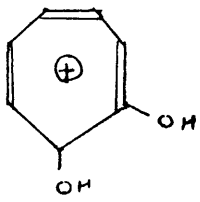

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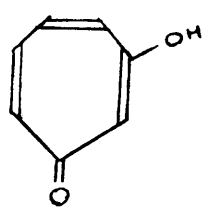

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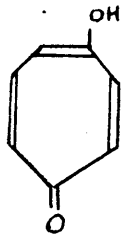

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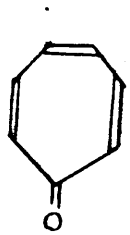

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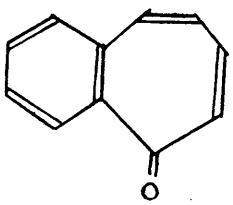

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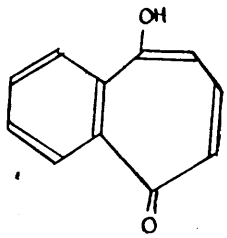

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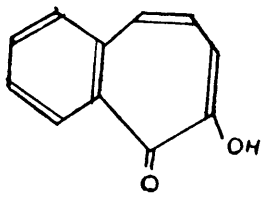

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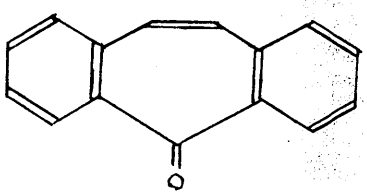

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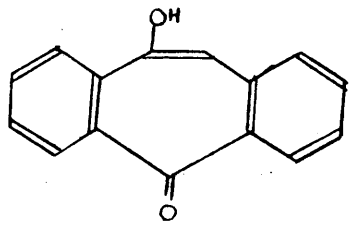

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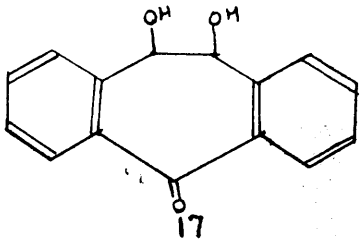

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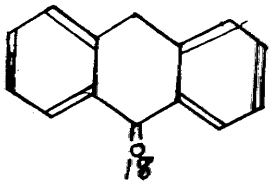

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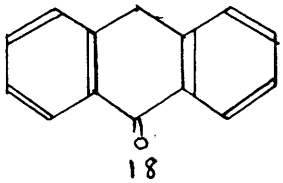

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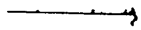

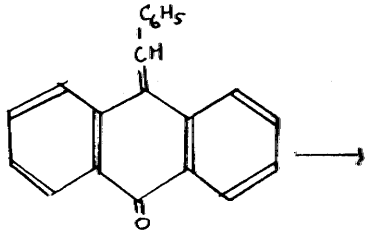

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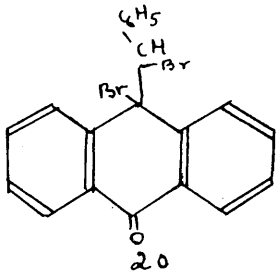

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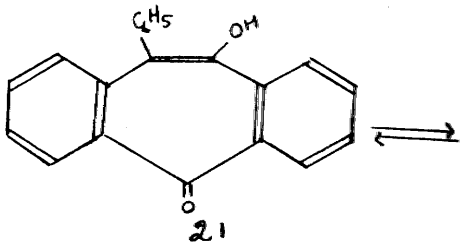

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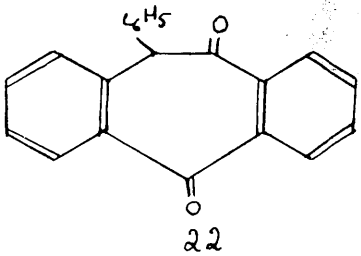

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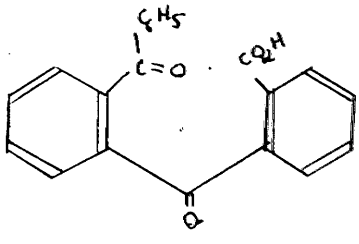

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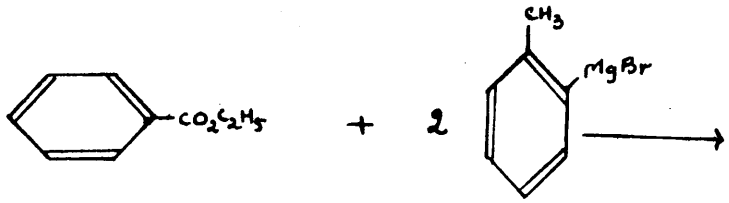

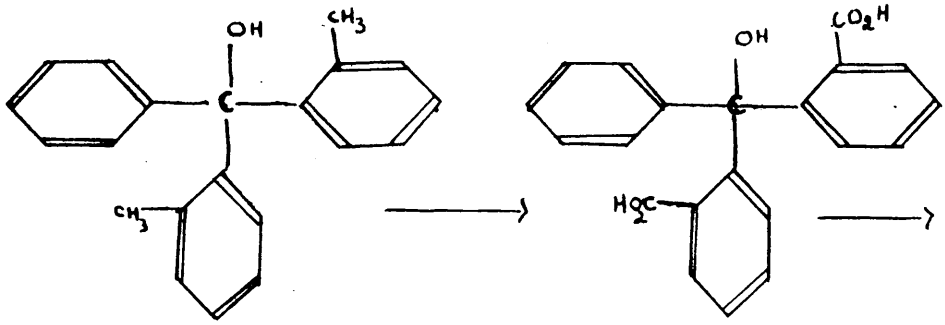

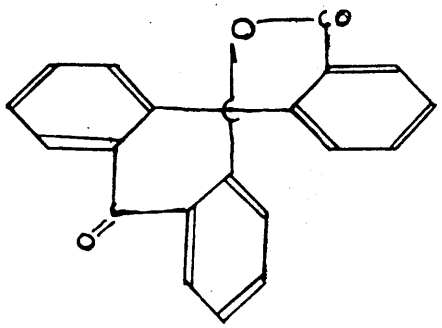

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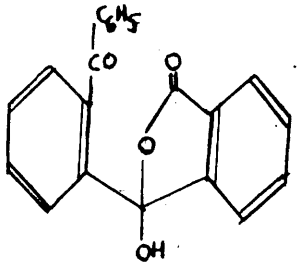

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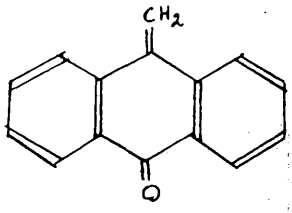

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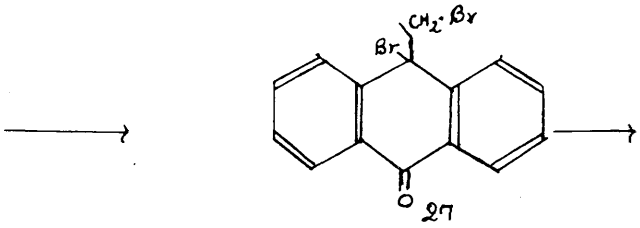

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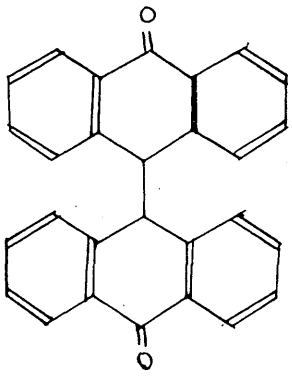

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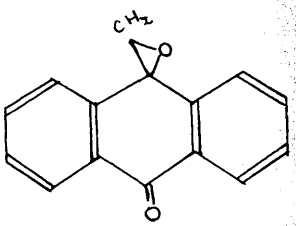

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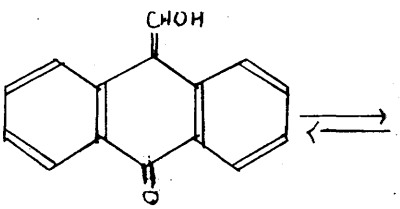

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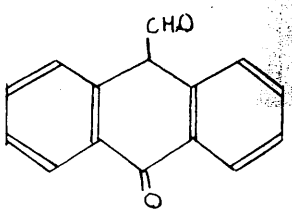

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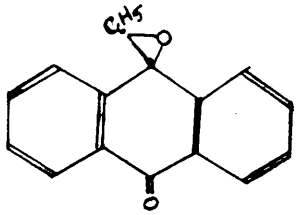

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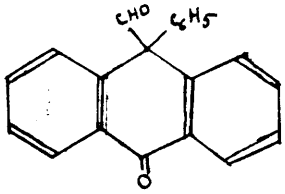

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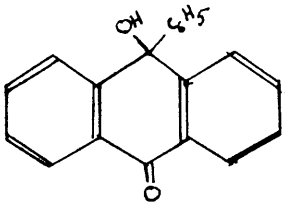

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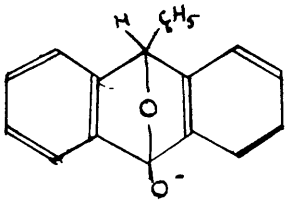

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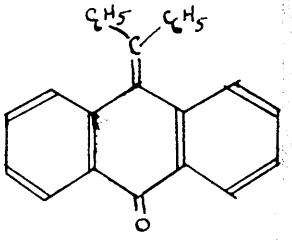

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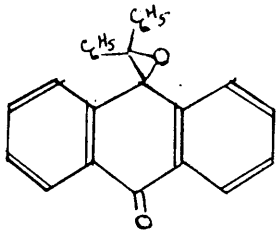

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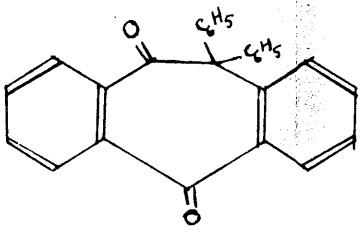

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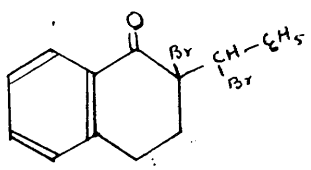

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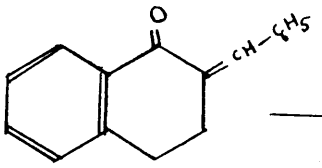

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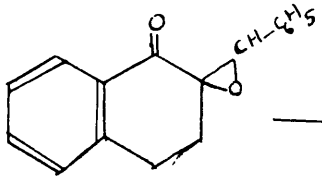

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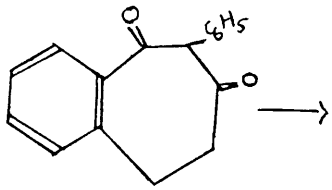

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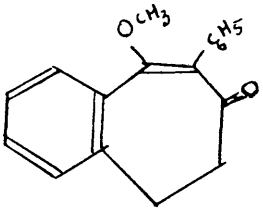

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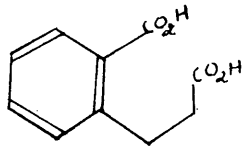

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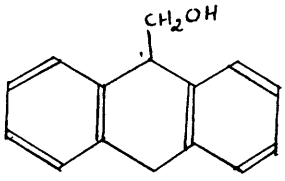

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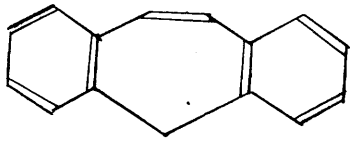

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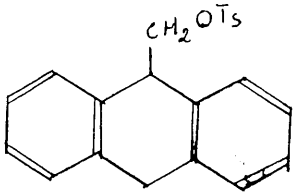

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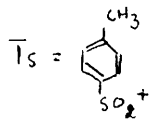

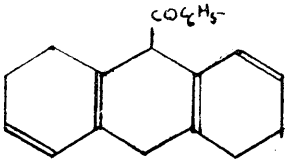

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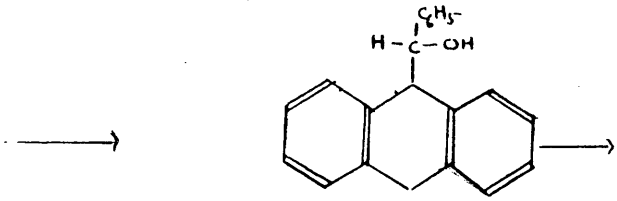

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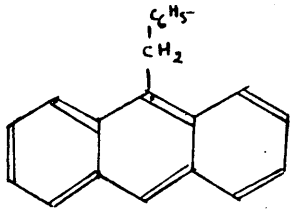

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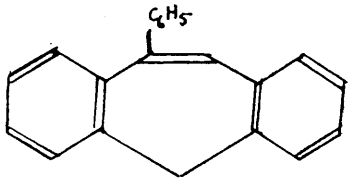

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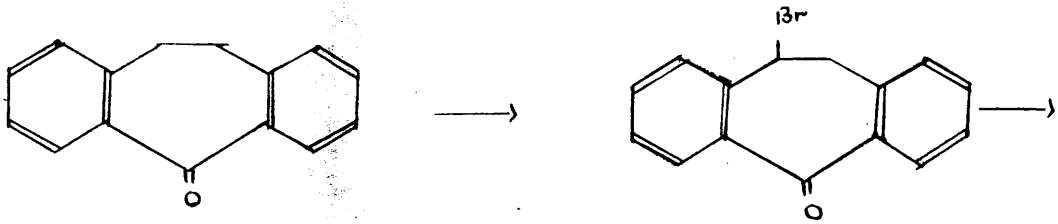
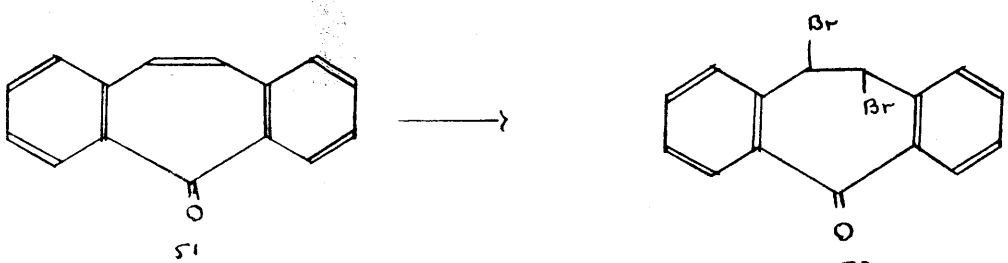
Scheme 6





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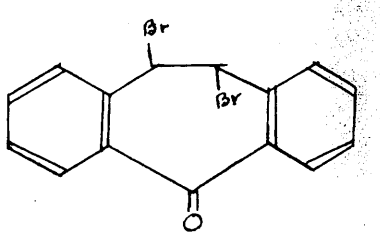

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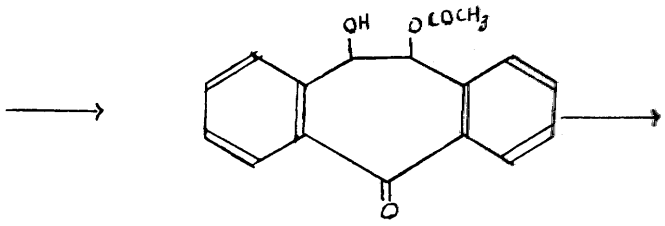

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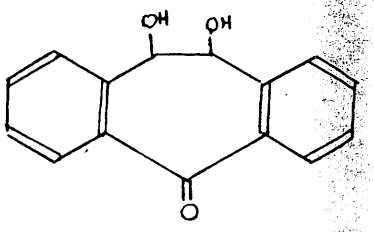

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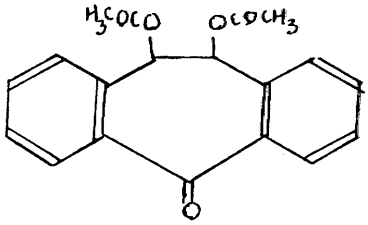

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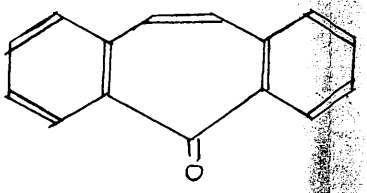

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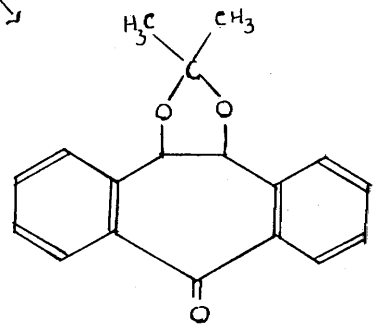

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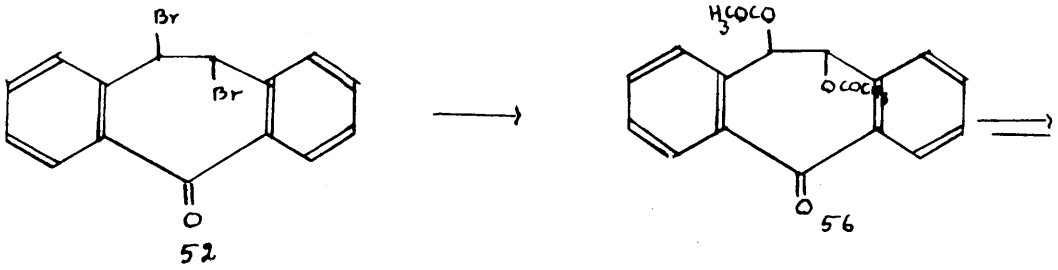
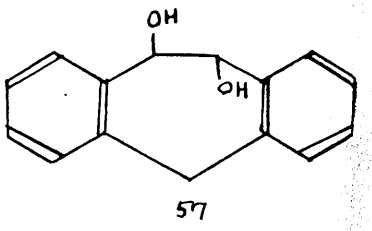
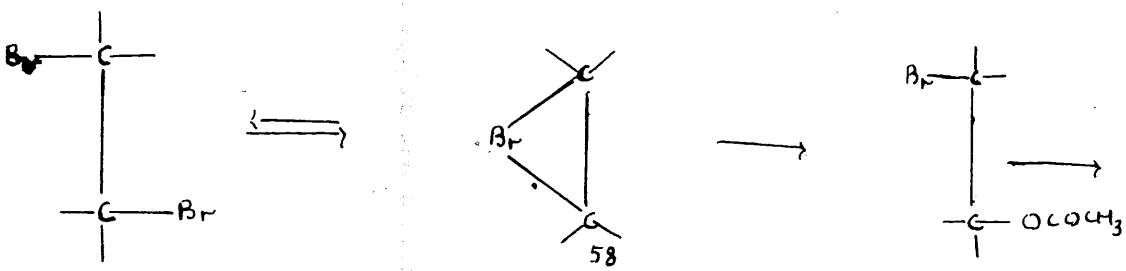

Br
Br
O
52
H3COCO
OCOCH3
O
56


OH
OH
57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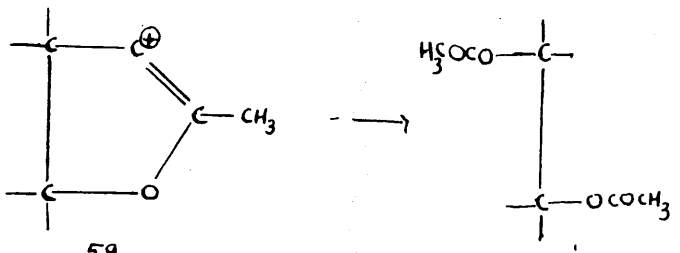
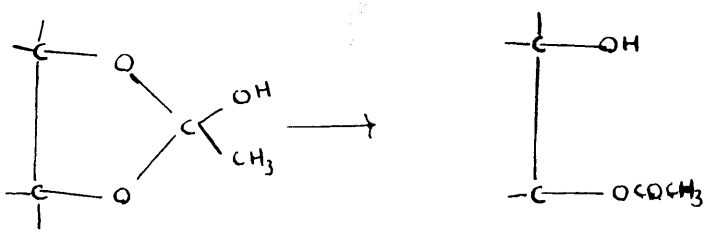
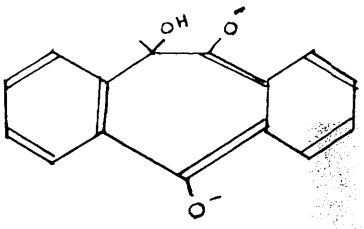
C
C
Br
Br
C
C
58
Br
C
C
OCOCH3


C
CH3
O
59
H3COCO
C
C
OCOCH3


O
OH
C
CH3
O
C
OH
C
OCOCH3

60



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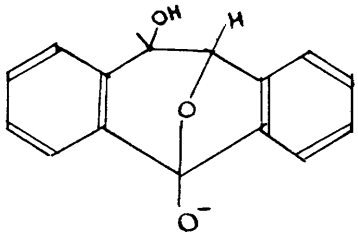

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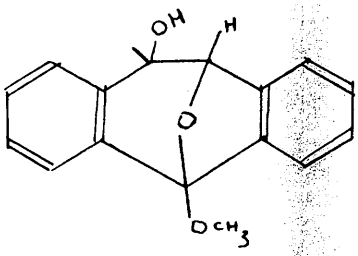

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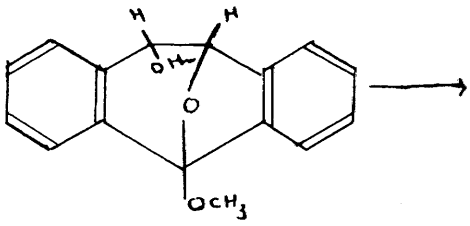

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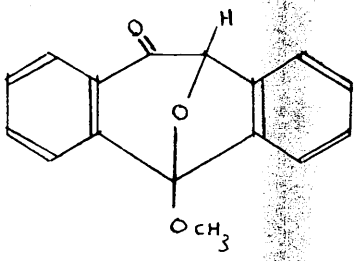

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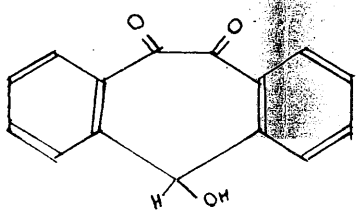

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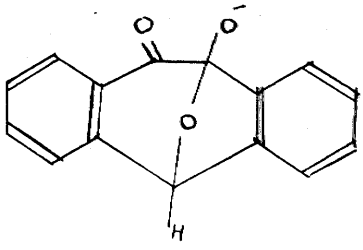
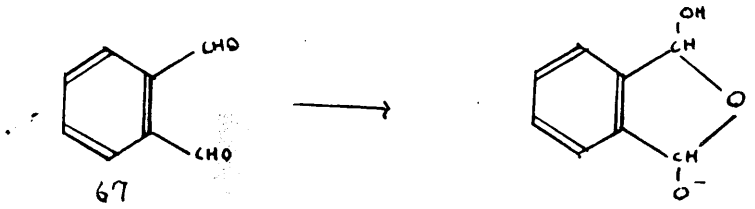
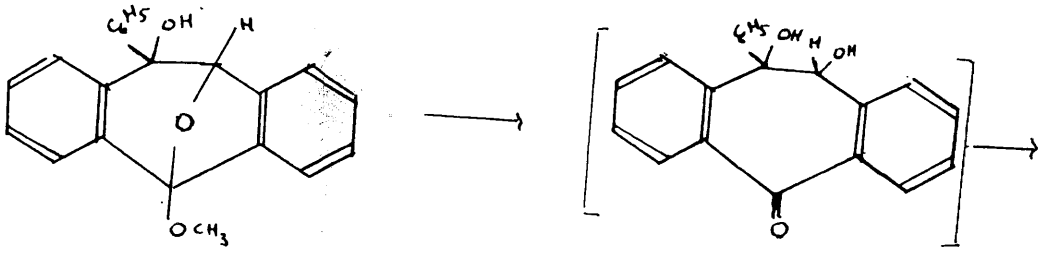
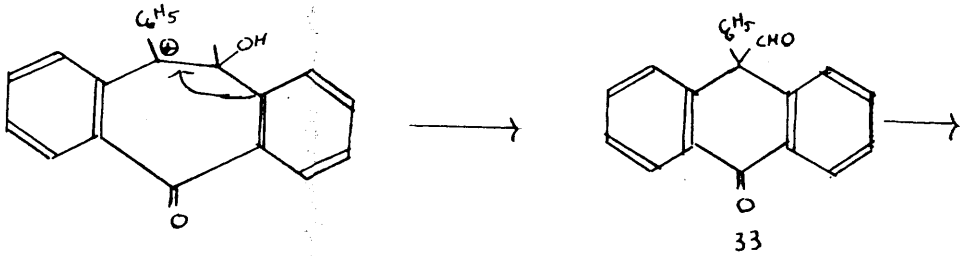



CHO
CHO
OH
CH
O
CH
O⁻

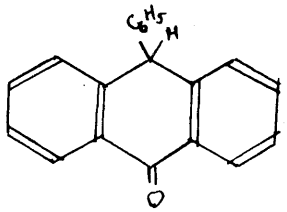
67


C6H5
OH
H
O
OCH3
C6H5
OH
H
OH
O

68 69

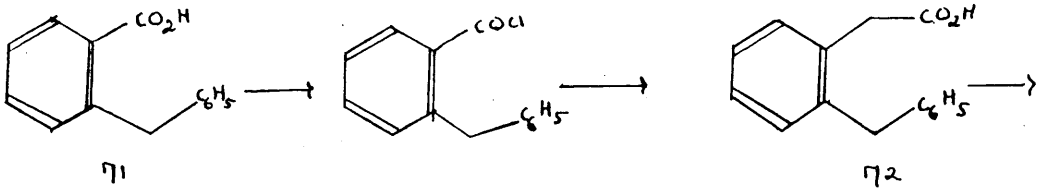

C6H5
OH
O
C6H5
CHO
O

33

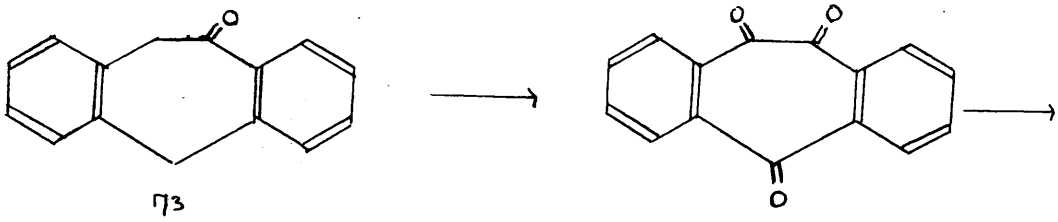

C6H5
H
O

70

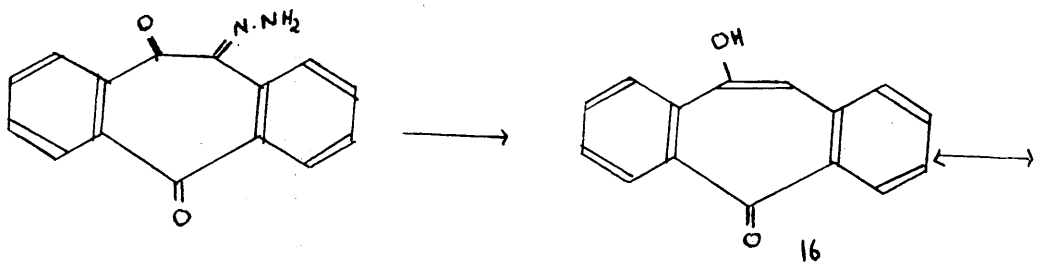
Scheme I



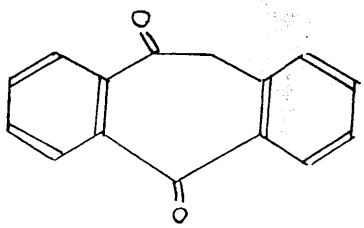
71 72



73 74



16



16A

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PAGE TWO

INTRODUCTION AND DISCUSSION

(Formula flow sheets for this section on pages 93 -107).

The bicyclic sesquiterpene, caryophyllene has been assigned the structure (1) as a result of the elegant investigations of Ruzicka, Barton, Sorm and Robertson [1-11]. This extremely interesting structure has not yet been synthesised and in fact, there are surprisingly few synthetic attempts recorded in the literature.

In 1957, Sorm and his co-workers[10] synthesised 4:8:11:11-tetramethyl-bicyclo (7:2:0) undecane (2), i.e. caryophyllane, by the following route. Trans-homo-caryophyllenic acid (3) was converted to the diacid chloride (4) and then, by treatment with diazoethane to the dimethyl-bis-diazoketone (5). Treatment of the bis-diazoketone with benzyl alcohol and collidine gave the required acid (6). Partial hydrolysis of its dimethyl ester gave a mixture of half esters (7 a,b). This mixture was converted to the ester-chloride mixture (8 a,b) and thence to the mono-diazo-ketones (9 a,b). Rearrangement of the diazo-ketones as above, hydrolysis and subsequent esterification gave a mixture of the two dimethyl esters (10 a,b). This mixture was subjected to an intra-molecular acyloin cyclisation and the acyloin mixture subjected to a Clemmensen reduction. Purification of this product afforded caryophyllane (2) identical, in physical properties and infra-red spectrum, with caryophyllane obtained by hydrogenation of caryophyllene.

An interesting approach to the nine-membered ring moiety of caryophyllene has been described recently by Brown[12]. 8-Carbethoxy-4-methyl-4,9-hydrindan-5-one (11) was prepared by treatment of 2-(3^1-keto-n-butyl)-2-carbethoxy-cyclopentenone with concentrated sulphuric acid. Catalytic

reduction of the double bond furnished the trans-hydrindanone (12) The ester group was then reduced to the alcohol (13) and converted to the p-toluene-sulphonate ester (14). It was hoped that treatment of this system with base would produce a series of electron shifts and result in the formation of the cyclononenone (17). However on treatment with base, the tobylate (14) was converted into a mixture of largely 6-methyl-bicyclo (4,3,1,$0^{1,5}$) decan-7-one (15) and 6-methyl-tricyclo (6,1,1,$0^{1,5}$) decan-7-one (16). Only the former product condensed with ethyl formate and hence the two products were easily separated.

A unique feature of the caryophyllene structure (1) is the 1:3-arrangement of a methyl-substituted endo double bond and an exo-methylene group in a cyclononene ring. Cope [13, 14] has synthesised cyclo-oct-1-ene-1:5-di-carboxylic acid (19) by treatment of 1-carbethoxy-bicyclo (3:3:1) non-3-one-9-one (18) with base. It was thought that the application of this type of ring cleavage to 1-carbethoxy-5-methyl-bicyclo (4:3:1) dec-3-ene-10-one (20) would furnish 1-methylcyclonon-2-one-1:5-di-carboxylic acid (21) which on suitable modification would give the 1-methyl-5-methylenecyclonon-1-ene moiety (22) of caryophyllene. In order to test this hypothesis, a series of model experiments were carried out using the more accessible 2-methylcyclohexanone as the starting material. 2-Carbethoxy-6-methylcyclohexanone was prepared by treatment of 2-methylcyclohexanone with diethyl oxalate followed by pyrolytic decarbonylation. Following the method developed by Cope [13, 14], a Michael reaction between this keto-ester (23) and acrolein yielded the aldehydo-keto-ester (24), which was then treated with concentrated sulphuric acid to furnish 1-carbethoxy-5-methylbicyclo-(3:3:1) non-3-ene-9-

-one 26, R=Et) in acceptable yield. (Two by-products were isolated at this stage; the structure and possible mode of origin of these interesting compounds is discussed in a later section, See p.58). It was not possible to prepare a semicarbazone or 2:4-dinitrophenylhydrazone of this compound (26, R=Et) but the β-keto-ester grouping was characterised by the ready formation of the pyrazolones (27, R=H; R=$CONH_2$; R=2:4-dinitrophenyl) and the iso-oxazolone (28).

Several attempts were now made to convert the keto-ester (26, R=C_2H_5) into 1-methyl-cyclo-oct-2-ene-1:5-dicarboxylic acid (29)using sodium ethoxide in ethyl alcohol. The sole product from this reaction proved to be 1-carbethoxy-5-methylbicyclo (3:3:1) non-3-ene-9-ol (26A, R=C_2H_5). This result is best explained in terms of a base-catalysed hydride shift between ethyl alcohol and the 9-keto compound (26, R=C_2H_5) to furnish the 9-hydroxybicyclo (3:3:1) compound and acetaldehyde. When potassium tert-butoxide was substituted for sodium ethoxide in the above reaction, tert-butyl-5-methylbicyclo (3:3:1) non-3-ene-9-ol-1-carboxylate (26A, R=Bu^t) was obtained in good yield. Trans-esterification of the ethyl ester to the tert-butyl ester would furnish the required ethyl alcohol for the proposed hydride shift affording the hydroxy tert-butyl ester (26A, R=Bu^t). The keto ester (26, R=C_2H_5) was unaffected by vigorous treatment with sodamide in benzene.

If this step had been successful the proposed sequence of reactions envisaged was as follows: the 2:3-double bond in (29) is situated β:γ to the carboxyl grouping at C_1, hence decarboxylation of the diacid (29) would have produced 1-methylcyclo-oct-1-ene-carboxylic acid (30, R=H). Lithium aluminium hydride reduction of the methyl ester (30, R=CH_3) to the cyclo-octenol (31) followed by dehydration would have furnished 1-methyl-5-methylenecyclo-oct-1-ene (32). A similar reaction sequence to that outlined above (21 - 32) using 2-carbethoxy-7-methylcycloheptanone as starting material would then have produced the required 1-methyl-5-methylenecyclonon-1-ene (22).

During an examination of reactions which generate a carbonium ion at the C_7-position of bicyclo (2:2:1)-heptane, Van Tamelen and Judd[16] treated β-isocamphor (33) with sulphuric acid and isolated 2:2:3-trimethyl-cyclohex-3-ene-1-carboxaldehyde. The keto-ester (26, R= C_2H_5) was therefore reduced with sodium borohydride to a mixture of the corresponding epimeric alcohols (35). This system, however, was found to be completely inert to treatment with sulphuric acid. Such a difference in reactivity between the bicyclo (2:2:1) alcohol (33) and the bicyclo (3:3:1)alcohol (35) is probably due to the greater strain inherent in the (2:2:1) system as compared with the rigid but strainless (3:3:1) arrangement. If the α-aldehydo-ester (36) had been isolated from this reaction, deformylation followed by reduction of the ester function and dehydration would have produced the required cyclo-octene.

Another approach to the cyclononene (22) moiety of caryophyllene was undertaken using as its basis the elegant work of Stork and Landesman[17]. These authors have shown that the pyrrolidine enamine of cyclohexanone (37) on treatment with acrolein, undergoes a Michael-type reaction followed by cyclisation to furnish 2-N-pyrrolidino-bicyclo (3:3:1) nonan-9-one (38). When the methiodide of the bicyclic-ketone (38) was treated with aqueous base, the product proved to be 4-cyclo-octenoic acid (39).

We decided to carry out the same reaction sequence, using 2-methylcycloheptanone, in the hope of obtaining 1-methylcyclon-1-ene-5-carboxylic acid (40) which could then be modified as previously described into the required cyclononene (22).

A variety of conditions were used in an attempt to form an enamine

of 2-methylcycloheptanone, but all of them failed.

As a result of these set-backs to the synthesis of the nine-membered ring of caryophyllene, the work was abandoned at this stage.

The keto-ester (26, R=C_2H_5) was prepared by concentrated sulphuric acid treatment of the aldehydo-ester (24). During the work-up of this reaction, if the ethereal extracts were washed with water to approximately pH 7 instead of with sodium bicarbonate solution, and then evaporated to dryness, a highly crystalline compound was deposited in the residual oil to the extent of 8 - 10% of the total yield.

This rearrangement product was collected and recrystallised as colourless needles (m.p.227-229°) from ethyl acetate. Analysis figures were obtained consistent with the molecular formula $C_{11}H_{12}O_2$. The product exhibited infra-red absorption maxima at 1665 cms^{-1} with a broad band at 3300-2300 cms^{-1} (conjugated carboxyl); 1580 cms^{-1} (conjugated aromatic ring) and at 843 cms^{-1} (1:2:3:4 - tetra substituted benzene ring). The ultra-violet absorption spectrum showed maxima at 242 mμ (ε = 13,000) and 285 mμ (ε = 2,040; substituted benzoic acid). This carboxylic acid (41, R=H) was converted into the corresponding amide (42), m.p.179-179.5°, by treatment of the corresponding acid chloride with ammonia. This amide was then dehydrated to the corresponding nitrile (43) m.p.71-73°. 7-Methylindan-4-carboxylic acid, m.p.227-229°, was prepared by Fieser and Seligman (18) by hydrolysis of 7-methylindan-4-carboxamide, m.p.176-177.4°, which in turn was obtained from the partial hydrolysis of 7-methyl-4-cyano-indan, m.p.72.9-73.2°.

The above evidence was consistent with the structure, 7-methylindan-4-

carboxylic acid (41,R=H) for this interesting rearrangement product and confirmation of this view was found in the following reaction sequence. The methyl ester (41,R=CH_3) was reduced with lithium aluminium hydride to the corresponding alcohol (44) which on hydrogenolysis furnished 4:7-dimethylindan identical in boiling point, refractive index, infra-red and ultra violet absorption spectra, with an authentic sample prepared by Bntel [19].

The formation of 7-methylindan-4-carboxylic acid during the treatment of the aldehydo-ester (26,R=C_2H_5) with concentrated sulphuric acid may be explained by the following mechanism.

An internal aldol-cyclisation of the aldehydo-ester (24) furnished 1-carbethoxy-4-hydroxy-5-methylbicyclo-(3:3:1) nonan-9-one (25) which would then undergo straightforward dehydration to furnish the keto ester (26,R=C_2H_5). If, however, in the presence of concentrated sulphuric acid, the C_9-ketone was protonated, the intermediate Ketone conjugate acid (46) could give rise to the isomeric 1-carbethoxy-5-methyl-9-hydroxybicyclo (3:3:1) nonan-4-one (47) by a 1:3- hydride shift with loss of a proton.

An intermolecular,acid-catalysed hydride shift has been invoked by Deno et,al. (20) to explain the formation of acetone when a mixture of 2-butanone or cyclohexanone and 2-propanol was heated with sulphuric acid,(60%). A similar intermediate to the protonated C_9 Ketone (46), namely (53) has been suggested by Prelog [21] to explain the conversion of 1-hydroxy-8-methyl-cis-hydrindane-5-one (52) into 5-hydroxy-8-methyl-cis-hydrindane-1-one (54).

Since the hydroxyl function at C_9 in the β,-Keto-ester (47) is doubly

neopentyl, the formation of a carbonium ion there could result in a facile Wagner-Meerwein rearrangement followed by loss of a proton, to form, as an intermediate, the unsaturated keto-ester (49).

Acid catalysed rearrangements of ketones occur not only when a tertiary carbonium[22] ion can be formed in the migration of an alkyl group to the carbonyl carbon but also where primary and secondary carbonium ions would be required[23].

A rearrangement of this type when applied to the protonated form of the keto-ester (49), followed by loss of the γ-proton would produce the conjugated diene hydroxy ester (50) which on dehydration would be converted into ethyl-7-methylindan-4-carboxylate (41, R=C_2H_5). The fact that aromatic carboxylic esters are readily hydrolysed to the corresponding acids by concentrated sulphuric acid treatment[24] would then explain our isolation of 7-methylindan-4-carboxylic acid. The same aromatic acid was isolated from treatment of the liquid hydroxy keto-ester (25) with concentrated sulphuric acid.

When the hydroxy-keto-ester (25) was warmed in alkali with furfural, the product, which could not be rigorously purified, showed an ultraviolet absorption maximum at 320 mμ(ε=2,706). This maximum, coupled with the low extinction co-efficient, suggested the presence of a small amount of the furfurylidene derivative (monofurfurylidene derivative of 2-methylcyclohexanone has a max.320 mμ(ε= 22,000) of the isomeric hydroxy keto ester (47). The hydride shift necessary for the conversion of the alcohol (25) into the isomeric alcohol (47) could have been brought about either by the mineral acid used to cyclise the aldehydo ester (24) or by the base used in the furfurylidene derivative preparation. Unfortunately it was

impossible to isolate either the hydroxy-keto-ester (47) or furfurylidene derivative in a pure state.

1-Carbethoxybicyclo (3:3:1)non-3-ene-9-one (18) was prepared according to the method of Cope [13] but there was no indication of any rearrangement products from this simpler bicyclo-system.

After removal of the 7-methylindan-4-carboxylic acid contaminant, an infra-red spectrum of the crude keto-ester (26, R=C_2H_5) showed an anomalous maximum at 1667 cm^{-1} and its ultra-violet spectrum had a maximum at 250 . These facts were inconsistent with the bicyclo-structure (26, R=C_2H_5). The presence of a further impurity was suspected but fractional distillation did not achieve any noteworthy separation. However, careful chromatography of this crude material on alumina separated the keto-ester from the liquid material possessing the conjugated carbonyl chromophore and permitted the isolation of this rearrangement product in pure state. Since the keto-ester (26, R=C_2H_5) did not react with semicarbazide acetate in the cold, a much more efficient separation of the unsaturated keto-ester from the keto-ester (26, R=C_2H_5) was achieved by treating the original mixture with semicarbazide reagent. The pure unsaturated keto-ester was then obtained by treating the purified semicarbazone with dilute sulphuric acid in the cold, followed by normal ether extraction. By this method the rearrangement material was found to be present in the original mixture to the extent of approximately 4.2%.

The pure compound which analysed for the formula $C_{13}H_{18}O_3$ (five double bond equivalents) showed absorption maxima in the infra-red at 1725 cm^{-1} (carbethoxy) and 1667 cm^{-1} (unsaturated ketone) and 252 (= 12,000) in the ultra-violet. As already mentioned, the corresponding semicarbazone was prepared and also a dark-red 2:4-dinitrophenyl hydrazone, m.p. 138-140°, (max. 390 mμ; ε = 14,670). Hydrogenation over 10% palladium-charcoal resulted in the uptake of one molar-equivalent of hydrogen with the formation of the corresponding saturated keto-ester, $C_{13}H_{20}O_{31}$ which was transparent in the ultra-

violet, and showed infra-red absorption maxima at 1725 cm^{-1} (carbethoxy) and 1710 cm^{-1} (six ring ketone). Hydrolysis of this saturated keto-ester gave the corresponding liquid carboxylic acid, $C_{11}H_{16}O_3$, which when subjected to a Kuhn-Roth determination gave a value in agreement with the presence of one C-methyl grouping in the molecule. A mono-piperonylidene derivative of this saturated keto-ester was prepared indicative of a methylene grouping α-to the ketone function. A Clemmensen reduction of the saturated keto-ester furnished, in acceptable yield, the parent ethyl ester which showed a maximum in the infra-red at 1725 cm^{-1}.

The parent unsaturated keto-ester was hydrolysed under extremely mild conditions (methanolic potassium hydroxide at room temperature) to the corresponding crystalline unsaturated keto-acid which smoothly underwent decarboxylation at 120° to give a liquid product ($C_{10}H_{14}O$) with infra-red absorption maxima at 1712 and 1660 cm^{-1}. Since this mixture gave only one conjugated 2:4-dinitrophenylhydrazone, m.p. 172-174°, (λmax. 390 mμ; ε=11,400) in quantitative yield, the deduction was made that either the molecule contains a vinylogous β-keto-acid system which had decarboxylated to give a mixture of conjugated and unconjugated unsaturated ketones, or else the double bond was situated $\beta:\gamma$ to the carboxyl group and in this case decarboxylation has resulted in the formation of a conjugated unsaturated ketone which was in equilibrium with a more stable non-conjugated unsaturated ketone. When this mixture of unsaturated ketones was hydrogenated over 10% palladium-charcoal, one molar - equivalent of hydrogen was absorbed and the resultant sweet smelling oil was transparent in the ultra-violet but

showed a single maximum at 1710 cm^{-1} (six ring ketone) in the infra-red, and gave a yellow 2:4-dinitrophenylhydrazone in good yield.

At this stage, the evidence for the structure of the unsaturated keto-ester was consistent with any one of three possible formulae (11), (55) and (56), which can be derived from the intermediate (47) by complex skeletal rearrangements.

4-Methyl-8-carbethoxy-$\Delta^{4,7}$-hydrindan-5-one (11) has been synthesised by Brown[12] and showed an ultra-violet absorption maximum at 247 mμ (ε=12,000). The infra-red spectrum of an authentic sample showed identical maxima at 1725 and 1667 cm^{-1} but differed markedly in the "finger-print" region when compared with the spectrum of our unsaturated keto-ester. In addition a mixed melting point of the 2:4-dinitrophenylhydrazone of (11), m.p. 135.5-138° and that derived from the rearrangement product (m.p. 138-140°) showed a marked depression. Any possibility that the structure of the two compounds might differ only in the position of the carbethoxyl function was dismissed when the 2:4-dinitrophenylhydrazone of the unsaturated ketone(57), prepared from the unsaturated keto-ester by hydrolysis and decarboxylation, showed a marked depression in melting point on admixture with the 2:4-dinitrophenylhydrazone prepared from the decarboxylated rearrangement product.

Work is still in progress to differentiate between the other two possible structures (55) and (56). A possible mechanism for the formation of (56) involves an acid-catalysed rearrangement of the hydroxy-ester (47) followed by a retro-aldol reaction to furnish the dione ester (58) which on cyclisation could furnish (56) instead of (11).

An alternative mechanism could give rise to the other possible

structure (55). The protonated form of the keto-ester (47) on rearrangement as shown (51-62) would furnish the isomeric 1-carbethoxy-6-methyl-9-hydroxybicyclo (4:2:1) nonan-5-one (62). Formation of a carbonium ion at C_9 followed by an acyl shift and subsequent proton loss would then furnish the alternate structure (55) for the unsaturated keto-ester.

Because of the interesting rearrangement products encountered during the conversion of the aldehydo ester (24) into the bicyclo keto-ester (26, R=C_2H_5), it was decided to synthesise the nor-aldehydo-ester (64) and examine its cyclisation to 1-carbethoxy-5-methyl-6-hydroxybicyclo (3:2:1) octan-8-one (65). An additional reason for examining this system lay in the structural similarity of this system to that of the bicyclo (4:2:1) moiety of longifolene (review of longifolene chemistry on p. 67). A suitably designed synthesis of (65) could undoubtedly be extended and modified to afford 1:5:5-trimethyl-8-hydroxy-bicyclo (4:2:1) nonan-9-one (7°) which is an obvious precursor for a synthesis of longifolene.

Previous synthesis of the bicyclo (3:2:1) system (see literature survey p.70) were unsuitable for elaboration to the hydroxy keto-ester (65) with its double bridge-head substitution, so the hydroxy keto-ester (65) was synthesised by the following route. 2-Carbethoxy-2-allyl 6-methylcyclohexanone (63) was prepared by alkylation of 2-carbethoxy-6-methylcyclohexanone with allyl bromide in the presence of sodium ethoxide. Ozonolysis of the keto-ester (63) in methylene chloride solution at -60°, then furnished formaldehyde and the aldehydo ester (64).

Various acid-catalysed internal aldol cyclisations of the type used in the bicyclo (3:3:1) system were all unsuccessful, e.g. treatment of the aldehyde-ester (64) with concentrated sulphuric acid, dilute hydrochloric acid/acetic acid, or dilute hydrochloric acid dioxan all resulted in the formation of intractable gums.

The required hydroxy ester (65) was prepared by shaking a suspension of the aldehyde ester (64) in aqueous base for twenty-four hours. Acidification* of this alkaline solution afforded an oily carboxylic acid which was esterified with diazomethane. The resultant liquid ester was then distilled and then triturated with petroleum-ether (60-80°) to furnish (65), m.p. 114-115° in poor yield. This alcohol showed infra-red absorption maxima at 3440 cm^{-1} (hydroxyl), 1745 cm^{-1} (carbomethoxy) and 1710 cm^{-1} (cyclohexanone). The corresponding p-toluenesulphonate was prepared, m.p. 85-87°.

Constant ether extraction of the original acidic reaction mixture furnished a crystalline hydroxycarboxylic acid which on esterification with diazomethane furnished the stereoisomeric hydroxy ester (65). This alcohol exhibited infra-red absorption maxima at 3510 cm^{-1} (hydroxyl), 1735 cm^{-1} and 1710 cm^{-1}. The corresponding p-toluenesulphonate was prepared, m.p. 146-147°. Oxidation of both these isomeric alcohols furnished the same diketone (66), m.p. 102-103°, thus confirming that the two alcohols differed only in their configuration at C_6. This diketone showed two maxima in the infra-red at 1755 cm^{-1} and 1715 cm^{-1}.

Treatment of the liquid isomer with concentrated sulphuric acid resulted in the formation of the bicyclo-lactone (67), m.p. 102-103°. The infra-red spectrum of this compound (in CCl_4 solution) showed a

single high intensity maximum at 1740 cm^{-1} (lactone + carbomethoxy). Hydrolysis of this lactone ester gave 4-methylcycloheptl-ene-1:4-dicarboxylic acid. Because of the poor yield of the solid hydroxy ester (65) this dehydration experiment was carried out only on the liquid isomer.

Mild treatment of both alcohols (65) with phosphorus oxychloride in pyridine in an attempt to form the compound (68) furnished the chloro keto ester (69). The formation of the same chloro compound from two stereoisomeric alcohols may be due to two different reaction mechanisms being involved, one with inversion and the other with retention of configuration at C_6.

A synthesis of the bicyclo (3:2:1) system (68) by dehydration of the alcohols (65) is still under active investigation as is a synthesis of the corresponding bicyclo (4:2:1) system.

LONGIFOLENE REVIEW:

Simonsen [25] first undertook the study of the Pinus longifolia oleoresin in 1920. Careful distillation techniques afforded α- and β-pinene, a bicyclic terpene and a tricyclic sesquiterpene hydrocarbon which was named longifolene. This compound was characterised by the derivatives which it formed with the hydrogen halides. On further investigation of longifolene Simonsen[26] found it to be resistant to oxidation with potassium permanganate. However the action of chromium trioxide in acetic acid or sodium dichromate in sulphuric acid furnished the isomeric longifolic and iso longifolic acid ($C_{14}H_{22}O_2$) respectively. Longifolic and iso longifolic acids are now considered to have the molecular formulae $C_{15}H_{22}O_2$[29,34] obtained from the oxidation of a terminal methylene grouping in the longifolene system.

Treatment of longifolene acid chloride with bromine converted it into iso longifolic acid. Simonsen proposed that the carboxyl function must be tertiary in nature because of the very slow esterification and saponification rates of longifolic acid and methyl longifolate respectively. At this time he also proposed a structure for longifolene which has since been shown to be erroneous.

Ozonolysis [27] of longifolene followed by oxidative decomposition of the ozonide yielded formaldehyde and an acid termed α-longifolic acid which was isomeric with longifolic and isolongifolic acid. It has since been shown [34] that longifolic and α-longifolic acids are not homogeneous acids but are mixtures predominating in isolongifolic acid. This evidence was taken at the time to be indicative of a vinyl grouping in longifolene. Although there was some progress being made in the

purely chemical approach to the structure of longifolene, the elegant X-ray studies of Moffett and Rogers[28] on longifolene hydrochloride and hydrobromide showed the true structure of longifolene to be (72).

Recent chemical evidence[29-33] has supplied confirmation of this structure. The infra-red absorption spectrum of longifolene showed maxima at 3125; 1666, and 871 cms^{-1} indicative of a cyclo pentan-exo-methylene double bond. Treatment of longifolene with osmium tetroxide furnished a glycol which was cleaved by lead tetra acetate to formaldehyde and a ketone (73) which showed a maximum in the infra-red at 1740 cms^{-1} (5 ring ketone). The same ketone (73) was prepared from longifolene by ozonolysis or chromium trioxide oxidation. The tricyclic ketone (73), which did not give any carbonyl derivatives even under forcing conditions, was completely unaffected by selenium dioxide, bromine and cold potassium permanganate. Refluxing the ketone in xylene with sodamide converted it into the corresponding amide $C_{14}H_{22}ON$. This evidence was interpreted as indicating the positions α to the $>CH_2$ grouping in the cyclopentane ring of longofolene to be either fully substituted or bridgehead positions.

Treatment of longifolene with hydrogen chloride afforded the corresponding hydrochloride which could be reconverted into longifolene by heating with silver acetate/acetic acid or sodium hydroxide /ethylene glycol. Hydrogenolysis of longifolene hydrochloride gave a hydrocarbon which had physical constants and spectra different from those of longifolene obtained by catalytic hydrogenation of longifolene. These results were explained on the basis of a Wagner-Meerwein rearrangement (74, 75). The secondary nature of the halogen atom was proved by the following reaction sequence. The longifolene hydro-

bromide magnesium derivative was converted into the corresponding alcohol which on oxidation gave a ketone $C_{15}H_{24}O$; infra-red maximum $1740^{cm^{-1}}$ (five ring ketone). This ketone was not attacked by selenium dioxide, bromine or cold alkaline permanganate.

The similarity in these reactions between camphene and longifolene led Curiasson to postulate the structure (72) for longifolene. This structure can be regarded as an elaboration product of camphene; a third isoprene unit having its tail joined to the exo-member of the gem-dimethyl grouping of camphene and its head (which in β-santalene (77) is free) linked to give the seven-membered ring of longifolene. As already mentioned this postulated structure (72) for longifolene was confirmed by the X-ray work of Moffett & Rogers[28]. On the basis of molecular rotation studies Curiasson has suggested that (+) longifolene was derived from (+) camphene and hence (72) represents the absolute configuration of longifolene.

BICYCLO (3:2:1) OCTANE SYSTEM REVIEW.

(Formula flow sheets for this review on Pages 103-109.

In 1907, Willstater and Veraguth[35] reported that a bromobicyclo-octane ($C_8H_{13}Br$) was formed during the preparation of α-cyclooctadiene dihydrobromide. No structure was assigned to this compound but these authors mentioned that treatment with quinoline at 150° produced a bicyclo octene.

The first simple route to bicyclo (3:2:1) octanes was devised by Alder and Windemuth[36]. Hydrogenation of the adduct of cyclopentadiene (78) and allylamine furnished 2:5-endomethylenhexahydrobenzylamine (79). Treatment of this amine with hydrochloric acid and nitrous acid gave bicyclo (3:2:1) octan-2-ol (80).

When Ipatieff and his co-workers [37] heated limonene with silicophosphoric acid to an elevated temperature, they isolated a new terpene which they identified as 2:6-dimethylbicyclo (3:2:1) oct-2-ene (81). This olefin on catalytic hydrogenation was converted into the hydrocarbon (82). Oxidation of the bicyclo-olefin (81) with selenium dioxide furnished the aldehyde (83) which on hydrogenolysis gave the hydrocarbon (86). This hydro carbon was also obtained from oxidation of the alcohol (84) to the ketone (85) with chromic acid followed by Wolf-Kishner reduction of the ketone (85). Proof of the structure of hydrocarbon (86) was obtained by its synthesis as shown in Scheme A.[38, 39].

In an attempt to find a convenient preparation of camphenilone, Hückel and Hartmann [40] oxidised camphene with lead tetra-acetate,

saponified and reduced the resulting enol acetate (thought to be that of camphenilone carboxaldehyde) and obtained two stereoisomeric alcohols which were assigned the structure (87). Braucker[41] proved that these alcohols were in fact (88) by oxidising them to camphenic acid.

Doering and Farber[42] prepared 2-bromobicyclo (3:2:1) octane (90) by the brominative decarboxylation of bicyclo (2:2:2) octane-2-carboxylic acid. The structure (90) was assigned to this product on the following evidence. Reduction of the bromo compound furnished bicyclo (3:2:1) octane (91) and treatment of the bromo compound with aqueous alkali furnished the bicyclo alcohol (80) previously prepared by Alder and Windemuth[36]. This interesting rearrangement of a bicyclo (2:2:2) system into a bicyclo (3:2:1) system prompted examination of the reaction between silver bromide and the potentially initial 2-bromo bicyclo (2:2:2) octane. Doering and Farber found that on treatment with silver bromide or silver acetate in bromine the bromide (90) was converted into the tricyclic alcohol (80). This rearrangement affords strong evidence for the hypothesis that silver bromide is a Lewis acid of sufficient strength as to weaken measurably the C-Br. bond of an alkyl bromide.

Newman[43] has prepared bicyclo (3:2:1) octan-2-one (93) by carrying out an intra-molecular alkylation of the bromoketone (92). This ketone could be reduced to the corresponding alcohol and vice versa. The alcohol was also prepared by the hydration of bicyclo-octene (94) with concentrated sulphuric acid.

In 1951 Farnam[44] obtained 3-hydroxynortricycline from the treatment of 2-aminobicyclo (2:2:1) hept-5-one with nitrous acid. Wildman and

Saunders [45] during an examination of the possible rearrangement of 2-aminobicyclo (2:2:2) oct-5-ene (95) to tricyclo (2:2:0) octan-3-ol (96), found that the amine (95) rearranged to 2-hydroxybicyclo (3:2:1) oct-3-ene (97). The structure of octene-alcohol (97) was confirmed by reduction to the known alcohol (80).

Alder and Heubke[46] have studied rearrangement of both exo and endo 2-methylaminobicyclo (2:2:1) heptanes with nitrous acid. The endo-isomer (98) gave the alcohol (80) in 67% yield while the exo-isomer (99) gave a mixture of the alcohols (80) 40%; (100) 27% and (101) 10-20% which could all be oxidised to the corresponding ketones. The ketone (93) gave the triketone (102) on oxidation with selenium dioxide.

Youseff et al[47] have prepared the two isomeric alcohols (80) and have ascribed their configuration as shown. The infra-red spectrum of bicyclo (3:2:1) octan-2-one showed an absorption maximum at 1715 cms^{-1}, therefore the ketonic ring is a cyclohexane and not a cycloheptane. Thus agreed these authors that the cyclohexane ring in the bicyclo (3:2:1) octan-2-one could only exist in the chair conformation in which the C_1 and C_3 carbon atoms are linked necessarily axially to form a dimethylene bridge. A study of the various possible conformations of this system led the authors to the conclusion that the chair conformation of the bicyclo (3:2:1) system as shown was the most stable.

Most of the bicyclo (3:2:1) octanes mentioned in the literature have been formed by rearrangement reactions, however bicyclo (3:2:1) octan-8-one (106) was isolated in 1% yield during the synthesis of

spiro compounds.[4] 2-Carbethoxycyclopentanone was condensed with 1:3-dibromopropane to form the product (103) which, after decarbethoxylation to the bromo-ketone (104), was cyclised to give the spiro ketone (105) in larger amount along with a low yield of the bicyclo (3:2:1) octanone (106).

A novel ring-enlargement has been reported by Stork and Landesman[17] when the enamine of cyclopentanone was treated with acrolein, 2-N-pyrrolidinobicyclo (3:2:1) octan-8-one (107) was formed in good yield. The methiodide of this compound on treatment with base furnished cyclohept-1-ene-1-carboxylic acid (108).

EXPERIMENTAL.

2-Methyl-6-carbethoxycyclohexanone (23).

A mixture of 2-methylcyclohexanone (200g.) and ethyl oxalate (300g.) was cooled to -10° and added dropwise with stirring to a solution of sodium (40g.) in dry ethanol (650 ml.) held at -10 to -15°. The resultant red solution was allowed to stand overnight in an ice-chest and then for eight hours at room temperature. The product was isolated by pouring the reaction mixture onto ice and acidifying with concentrated hydrochloric acid (80 ml.). The precipitated yellow oil was extracted with ether, the ethereal extract washed with water sodium bicarbonate solution, water, and then dried over magnesium sulphate. Removal of the ether under reduced pressure, furnished a thick oil which was heated at 180-200° for six hours until no more carbonmonoxide was evolved. A practical distillation then furnished 2-methyl-6-carbethoxy cyclohexanone , b.pt. 110-113°/11 mm. $\mu_D^{25°}$ 1.466.

β-(1-Carbethoxy,2-keto-3-methylcyclohexyl) propionaldehyde.(24).

A mixture of 2-methyl-6-carbethoxycyclohexanone (5.52g.) and redistilled acrolein (1.98 ml.) was added dropwise, with stirring, to a solution of sodium (0.032g.) in anhydrous ethanol (20 ml.) containing hydroquinone (0.035g.), chilled to -70°. After the addition, stirring was continued for one hour and then for a further thirty minutes at room temperature. Glacial acetic acid was then added till the reaction mixture was at pH7. Removal of the ethanol under reduced pressure furnished a viscous red oil which was dissolved in ether and the ethereal solution washed with water, dilute sodium bicarbonate solution, water and then dried. Removal of the solvent, followed by distillation furnished required aldehyde. b.p. 130°/0.4 mm. Found; C.64.85;

H, 8.15. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%.

The corresponding bis-2:4-dinitrophenylhydrazone was prepared and recrystallised from acetic acid in needles. m.p. 200-201°. Found; C,49.15; H,4.45; N,18.45. $C_{25}H_{28}O_{10}$ requires C,50.0; H,4.45; N,18.65%.

1-Carbethoxy-4-hydroxy-5-methylbicyclo (3:3:1) nonan-9-one (25).

A mixture of the above aldehyde (3.0g.) glacial acetic acid (12 ml.) concentrated hydrochloric acid (3.0 ml.) and water (6 ml.) was gently refluxed on a steam-bath for a short time and then held at room temperature for eighteen hours. The reaction mixture was then neutralised with sodium bicarbonate solution and the precipitated oil extracted with ether. The combined ethereal extracts were washed with water and dried over magnesium sulphate. Removal of the ether furnished a thick oil which distilled at 130°/0.05 mm. to furnish 2-carbethoxy-4-hydroxy-5-methylbicyclo (3:3:1) nonan-9-one as a colourless oil (2.4g; 80%). Found; C,64.65; H,8.7. $C_{13}H_{20}O_4$ requires C,64.95; H,8.4%.

The infra-red spectrum (liquid film) of this material showed a maximum at 3450$^{cms^{-1}}$ (hydroxyl) and no peak at 2720$^{cm^{-1}}$ (aldehyde).

1-Carbethoxy-5-methylbicyclo (3:3:1) non-3-ene-9-one (26, R=C_2H_5).

The above aldehyde (367g.) was added dropwise to concentrated sulphuric acid (1,000 ml.) held at 0°C. and the reaction mixture stirred overnight at room temperature. The dark red solution was cautiously poured into ice-water (15 l.) and thoroughly extracted with ether (2 x 5l.). The combined ethereal extracts were thoroughly washed with water, dried and the solvent removed under reduced pressure. The residual oil was then filtered to remove 7-methyl-

indan-4-carboxylic acid (10g.) and distilled to furnish a clean oil b.p. 120°/0.25 mm. - 140°/0.8 mm. (204g.). The infra-red spectrum (liquid film) of this material exhibited a strong band at 1650 cm^{-1} (conjugated carbonyl).

Chromatography of a sample of this crude distillate on alumina separated the required keto-ester (26, R=C_2H_5) as the petroleum-ether (60-80°) eluant, from the conjugated carbonyl material which was eluted with benzene as a colourless oil. This impurity exhibited bands at 1728 cm^{-1} (carbethoxyl) and 1667 cm^{-1} (conjugated carbonyl) in the infra-red and showed an ultra-violet maximum at 252 mμ (ε=12,000).

A solution of the crude distillate (204g.) in methanol (200 ml.) was treated with a concentrated solution of semicarbazide acetate (excess) in aqueous methanol and the reaction mixture allowed to stand at 0° overnight. The precipitated semicarbazone (21.25g.) was then filtered off, the filtrate concentrated to small volume under reduced pressure, diluted with a large volume of water and thoroughly extracted with ether. The combined ethereal extracts were washed with water, dried and the solvent removed under reduced pressure to afford a clear mobile oil which distilled at 115°/0.2 mm. $n_D^{21.5}$ 1.4900 to give pure 1-carbethoxy-5-methylbicyclo (3:3:1) non-3-ene-9-one (135g.). Found; C,69.8; H,8.15 $C_{13}H_{18}O_3$ requires C,70.25; H,8.15%. The infra-red spectrum of the pure keto-ester (26, R=C_2H_5) showed maxima at 1730 (carbethoxy) and 1710 cm^{-1} (cyclohexanone).

The corresponding 2:4-dinitrophenylpyrazolone (27, R=2:4 dinitro-phenyl) was prepared by refluxing keto-ester in ethanol, with Brady's reagent for two hours. The cooled reaction mixture deposited the crude pyrazolone as yellow needles which were collected and recrystallised in needles, m.p. 203-205° from benzene.

Found; C.57.5; H,f.1; N,15.9. $C_{17}H_{16}O_5N_4$ requires C,57.3; H,4.53; N,15.7%

The corresponding pyrazolone (27, R=H) recrystallised from benzene-petroleum ether (40-60°) in needles, m.p. 149-150°. Found; C,69.35; H,7.35; $C_{11}H_{14}O_2N_2$ requires C,69.45; H,7.40%.

The iso-oxazolone (28) prepared from β-keto-ester (26,R=CH_3) and hydroxylamine recrystallised from aqueous methanol in flakes, m.p.95-97°. Found; C,69.45; H,6.90; N,6.7. $C_{11}H_{13}O_2N$ requires C,69.1; H,6.85; N,7.35%.

The amido-pyrazolone, prepared from the keto-ester (26, R= C_2H_5) and semicarbbazide acetate as above, crystallised from water in needles, m.p. 157-162°. Found; C,62.1; H,6.45; N,17.9. $C_{15}H_{16}O_2N_3$ requires C,61.80; H,6.50; N,18.0.

Treatment of the 2-carbethoxy-4-hydroxy-5-methylbicyclo (3:3:1)-nonan-9-one with concentrated sulphuric acid as above gave the same mixture of products.

The semicarbazone (21.25g.) of the unsaturated keto-ester prepared above was quantitatively converted into the parent compound by shaking with sulphonic acid (6N) and ether. The ethereal layer was separated, washed with water, dilute sodium bicarbonate solution, water and dried. Removal of the solvent and distillation of the residual oil furnished the pure rearrangement product (15.5g.) as a colourless liquid, b.p. 107-112°/0.175 mm., $n_D^{21°}$ 1.5002. Found; C,70.35; H,7.7. $C_{13}H_{18}O_3$ requires C,70.25; H,8.15%. The infra-red spectrum (liquid film) of this material showed maxima at 1728 cm^{-1} (carbethoxyl) and 1667 cm^{-1} (conjugated carbonyl). The ultra-violet spectrum in ethanol showed a maximum at 252 mμ (ε-12,000).

The corresponding 2:4-dinitrophenylhydrazone was prepared and crystallised from methanol in plates, m.p. 138-140° λmax (chloroform)

390mμ (ε= 14,000). Found; C,56.70; H,5.60; N,14.5. $C_{19}H_{22}O_6N_4$ requires C,56.70, H,5.5; N,13.9%.

The corresponding semicarbazone recrystallised from methanol in needles. m.p.195-196° Found; C,60.3; H,7.7; N,14.7. $C_{14}H_{21}O_3N_3$ requires C,60.2; H7.6; N,15.05%.

5-Methylbicyclo (3:3:1) non-3-ene-9-one-1-carboxylic acid (26, R=H).

The pure keto-ester (26, R=C_2H_5) was refluxed in aqueous ethanolic sodium hydroxide (20 ml. 2N.) for three hours. The reaction mixture was then evaporated to dryness, the solid residue dissolved in water extracted with ether and the alkaline layer acidified to congo red with dilute sulphuric acid. The crude carboxylic acid was filtered off, dried and recrystallised from petroleum-ether (60-80°) to furnish the bicyclo keto acid in needles m.p. 139-140°. Found; C, 68.40; H,7.0; $C_{11}H_{14}O_3$ requires C,68.0; H,7.3%.

The corresponding methyl ester, which was prepared from the above acid and diazomethane, crystallised from methanol in cubes m.p. 83-84°. Found; C,69.4; H,7.9; $C_{12}H_{16}O_3$ requires C, 69.2; H,7.75%.

Treatment of 1-carbethoxy-5-methylbicyclo (3:3:1) non-3-ene-9-one (26, R= C_2H_5) with sodium ethoxide.

A solution of sodium (0.172g.) and the keto-ester (2g.) in anhydrous ethanol (25 ml.) was refluxed for twenty hours and then poured into water. The precipitated oil was extracted with ether and the ethereal extracts washed with water, dilute hydrochloric acid, dilute sodium bicarbonate solution water and then dried. Removal of the solvent and distillation of the residual oil furnished 1-carbethoxy-5-methylbicyclo (3:3:1) non-3-ene-9-ol as a colourless oil, b.p. 80°/0.05 m.m. Found;

C,69.4; H,8.8 $C_{13}H_{20}O_3$ requires C,69.6; H, 8.9%. The infra-red spectrum (liquid film) showed maxima at 3450$^{cms^{-1}}$ (hydroxyl) and 1725$^{cm^{-1}}$ (carbethoxy).

From the above sodium bicarbonate extraction 5-methylbicyclo (3:3:1) non-3-ene-9-ol-1-carboxylic acid was isolated by acidification and ether extraction. This acid crystallised from benzene/petroleum ether (40-60°) as flakes m.p. 168-169°. Found; C,67.3; H,7.9. $C_{11}H_{16}O_3$ requires C,67.3; H,8.2%.

Treatment of 1-carbethoxy-5-methylbicyclo (3:3:1) non-3-ene-9-one with potassium tert-butoxide.

When the above reaction was repeated using potassium tert-butoxide, the corresponding bicyclohydroxy-tert-butyl ester was obtained, which crystallised from aqueous methanol in flakes, m.p. 68-70°. Found; C,71.9; H,9.3. $C_{15}H_{24}O_3$ requires C,71.4; H,9.6%.

Treatment of 1-carbethoxy-5-methylbicyclo (3:3:1) non-3-ene-9-one with sodamide.

The keto-ester (26, R=C_2H_5, 1.1g.) was refluxed with sodamide (0.25g.) in benzene for four hours and then washed with water and dried. Removal of the solvent furnished the starting keto-ester or the corresponding amide which on hydrolysis gave the corresponding carboxylic acid, m.p. 137-138°.

1-Carbethoxy-9-hydroxy-5-methylbicyclo (3:3:1) non-3-ene (26A, R=C_2H_5)

Sodium borohydride (0.5g.) was added to a solution of the keto-ester 5g. 26, R= C_2H_5) in aqueous methanol (25 ml. 40%) and the reaction mixture allowed to stand at room temperature for twenty four hours. Dilution with water, followed by ether extraction in the usual manner

furnished the required alcohol (4g.) b.p. 83°/0.4 m.m.; $\mu_D^{22.5}$ 1.4915. Found; C,69.1; H,8.8. $C_{13}H_{20}O_3$ requires C,69.6; H,9.0%.

The corresponding 3:5-dinitrobenzoate crystallised from alcohol as microcrystalline solid, m.p. 114-115°. Found; C,57.35; H, 5.4; N,7.0. $C_{20}H_{22}O_8N_2$ requires C,57.4; H,5.3; N,6.7%.

This alcohol was recovered completely unchanged on treatment with dilute sulphuric acid.

2-Methylcycloheptanone (39A).

N-Nitrosoethylurethane (30g.) was added dropwise during one hour to a solution of cyclohexanone (20g.) in alcoholic potassium hydroxide (80 ml., 1.25%) held at 18-26°. After stirring for a further hour at room temperature the reaction mixture was evaporated under reduced pressure and the residue extracted with ether. The combined ethereal extracts were washed with dilute sulphuric acid, water, dried and the solvent removed to give an oil which on fractional distillation furnished 2-methylcycloheptanone (10g.) b.p. 102°/28 m.m.

Attempted formation of the enamine of 2-methylcycloheptanone and hence its reaction with acrolein.

A mixture of 2-methylcycloheptanone (11.2g.) and pyrrolidine (27.2g.) was refluxed in benzene (400 ml.) under a Dean and Stark water separator for five hours. The reaction mixture was evaporated under reduced pressure and the residual oil (supposed enamine) dissolved in dioxan (20 ml.) and treated with acrolein (2 ml.). This reaction mixture, after stirring for one hour at 5° was evaporated under reduced pressure, when 2-methylcycloheptanone was recovered unchanged.

The crude 7-methylindan-4-carboxylic acid, m.p. 225-228.5° isolated in the preparation of the keto ester (26, R= C_2H_5), was recrystallised

from ethyl acetate in stout prisms, m.p. 228-229°. Found; C,75.15; H,7.00. $C_{11}H_{12}O_2$ requires C,75.0; H, 6.85%. This compound exhibited infra-red absorption maxima at 1665 cm^{-1} with a broad band at 3300-2300 cm^{-1} (conjugated carboxyl), 1600, cm^{-1} 1580 cm^{-1} and 843 cm^{-1}. The ultra violet spectrum showed a maximum at 242 mμ (ε=13,000) and 285 mμ (ε= 2040) (substituted benzoic acid).

Methyl-7-methylindan-4-carboxylate (41, R=CH_3).

A suspension of the acid (41; R= H, 1.0g.) in ether was treated with a slight excess of an ethereal diazomethane until evolution of nitrogen had ceased and solution complete, then solution allowed to stand at room temperature for two hours. Evaporation of solvent afforded the ester as a thick oil (1.08g.) which rapidly solidified, and crystallised from aqueous methanol as colourless needles, m.p. 45-47°. Found; C,75.5; H,7.4. $C_{12}H_{14}O_2$ requires C,75.75; H,7.4%.

The product exhibited infra-red (nujol mull) absorption at 1715 cm^{-1} (aromatic carbomethoxyl), 1600 cm^{-1} and a medium band at 834 cm^{-1} (two adjacent free hydrogen atoms in an aromatic ring.) in nujol

7-Methylindan-4-carboxamide (42).

A suspension of the acid (41, R=H) in benzene was shaken with an excess of oxalyl chloride at room temperature for three hours. The filtered solution on evaporation to dryness afforded the acid chloride as a thick oil in poor yield. The product exhibited infra-red (liquid film) absorption at 1750 cm^{-1} and 776 cm^{-1} (aromatic acid chloride), 3000, 1600, 1585 cm^{-1} with a strong band at 776 cm^{-1} (aromatic ring with two adjacent free hydrogen atoms). The acid chloride was triturated with 0.880 ammonia affording the corresponding amide as colourless needles

m.p. 179-179.5° from ethyl acetate (lit.[18] 176-177.4°). Found: C, 75.2; H, 7.5; N,7.9. $C_{11}H_{13}NO$ requires C,75.4; H,7.5; N,8.0%

The product exhibited infra-red $\lambda_{max}^{(nujol\ mull)}$ absorption at 3330, 3170, 1650 and 1623 cm^{-1} (primary aromatic amide), 1603, 1585 cm^{-1} with a weak band at 829 cm^{-1} (aromatic ring with two adjacent free hydrogen atoms).

7-Methyl-4-cyanoindane (43).

An intimate mixture of the amide with the same wight of phosphorus pentoxide was warmed to 120° for fifteen minutes. Water was carefully added to the cooled mixture and the resulting solution extracted with benzene. The benzene extract was washed with water and dried over magnesium sulphate. Evaporation of solvent afforded the nitrile as colourless elongated plates, m.p. 71-73° from petrol (40-60°) (lit.[18] 72.9-73.2°). Found: N, 8.65. $C_{11}H_{11}N$ requires N, 8.9%. The product exhibited infra-red $\lambda_{max}^{(nujol\ mull)}$ absorption at 2225 cm^{-1} (aromatic nitrile), 3000, 1600 cm^{-1} with a very strong band at 820 cm^{-1} (aromatic ring with two adjacent free hydrogen atoms).

4-Hydroxymethyl-7-methylindane (44).

A mixture of lithium aluminium hydride (0.5g.) in dry ether (100 ml.) was refluxed gently for two hours. A solution of the ester (2.1g. 41; R=Me) in dry ether (15 ml.) was added slowly to the cooled mixture and then refluxed gently for two hours. The cooled mixture was decomposed by careful addition of dry ethylacetate and poured into ice-water (100 ml.) and acidified with dilute hydrochloric acid. The separated ethereal layer was washed with dilute sodium carbonate solution, water and dried over magnesium sulphate. Evaporation of solvent afforded the alcohol as a thick oil (1.65g.; 88%), solid at 0°.

The product exhibited infra-red (liquid film) absorption at 3300 and 1000 cm^{-1} (primary hydroxyl), 3000, 1600, 1493 cm^{-1} with a very strong band at 817 cm^{-1} (aromatic ring with two adjacent free hydrogen atoms).

4:7-Dimethylindane (45)

A solution of the alcohol (0.32g.[44]) in glacial acetic acid containing a few drops of perchloric acid was hydrogenated at 18° over platinum oxide, hydrogen (45 ml.) being absorbed within fifteen minutes. The solution was poured into a large volume of water and extracted with ether (4g.). Ethereal extracts were washed with dilute sodium bicarbonate solution, water and dried over magnesium sulphate. Careful evaporation of solvent afforded a mobile oil, fractionated at 11 mm. as a colourless oil, n_D^{22} 1.5290.

The product exhibited weak infra-red absorption bands at 2995 and 1600 cm^{-1} (aromatic) with a strong band at 1493 cm^{-1} (aromatic) and a very strong band at 807 cm^{-1} (aromatic ring with two free adjacent hydrogen atoms).

The product exhibited ultra-violet maximum in iso octane at 264 mμ (ε 231) with shoulder maxima at 258 and 272 mμ (lit. maxima 258, 265 and 273 mμ).

Hydrogenation of the unsaturated keto ester rearrangement product.

A solution of the unsaturated keto ester (3.05g.) in ethyl acetate (100 ml.) was hydrogenated using palladium-charcoal (10%) as the catalyst. The absorption of hydrogen ceased after an uptake of 336 ml. (one double bond equivalent). After filtration of the product, residual oil was fractionally distilled to give the corresponding saturated ketone b.p. 88-92°/0.15 mm., $n_D^{22.5}$ 1.4722. Found: C,69.3;

H,9.63. $C_{13}H_{20}O_3$ requires C,69.6; H,9.0%.

This compound was transparent in the ultra-violet but showed two maxima at 1725 cm^{-1} (carbethoxy) and 1712 cm^{-1} (six ring ketone).

The corresponding 2:4-dinitrophenylhydrazone crystallised from methanol in stout needles m.p. 111-112°. Found; C,56.6; H,5.40; N,14.1. $C_{19}H_{24}O_6N_4$ requires C,56.45; H,5.95; N,13.85%.

Hydrolysis of the saturated keto-ester prepared above.

A solution of the above keto-ester (1.56g.) and potassium hydroxide (1.37g.) in methanol (50 ml.) was refluxed for three hours and then evaporated to dryness. The residual solid was dissolved in water, extracted with ether to remove any neutral material and then acidified to congo red with dilute sulphuric acid. The precipitated oil was extracted with ether and the ethereal extracts washed with water, dried and the solvent removed under reduced pressure. The residual oil was distilled affording the saturated keto-carboxylic acid, b.p. 128-130°/ 0.07 mm.; n_D^{18} 1.4980. Found; C,67.1; H,8.4. $C_{11}H_{16}O_3$ requires C,67.3; H,8.2%. C-methyl determination; Found, 6.85; 1-C-methyl requires 7.65%.

Clemmenson reduction of the saturated keto-ester.

A solution of the saturated keto-ester (1g.) in benzene (20 ml.) was refluxed for nine hours with a mixture of amalgamated zinc (2g.), concentrated hydrochloric acid (100 ml.) and water (75 ml.). The organic layer was separated from the cooled reaction mixture which was then re-extracted with ether. The combined organic extracts were washed with saturated sodium carbonate solution, water, dried and the solvent removed under reduced pressure. The residual oil was dissolved in

methanol and treated with an excess of sodium borohydride. Isolation in the normal manner gave an oil which was chromatographed on alumina (grade I). Petroleum-ether (60-80°) elution afforded the parent ethyl ester as a sweet-smelling oil, (0.16g.) b.p. (oil bath temperature) 130°/11 mm., n_D^{21} 1.4610. Found: C,74.05; H, 10.8. $C_{13}H_{22}O_2$ requires C,74.23; H,10.55%.

The infra-red spectrum (carbon tetrachloride solution) exhibited a single maximum at 1725 cms^{-1} (carbethoxyl).

Mono-piperanylidene derivative of the saturated keto-acid.

A solution of the saturated keto-ester (0.224g.) and piperonal in ethanol (25 ml.), containing aqueous sodium hydroxide (1 ml. 1N); was warmed on a steam bath for one hour and then evaporated to dryness. The residual solid was dissolved in water, extracted with ether and then acidified with dilute sulphuric acid and re-extracted with ether. This latter ethereal extract was washed with water , dried and the solvent removed to furnish a thick oil which solidified on trituration with ether. The mono-piperanylidene-keto-acid so obtained recrystallised from benzene-petroleum ether (60-80°) in micro-prisms, m.p. 137-139°. Found; C,69.3; H,5.9. $C_{19}H_{20}O_5$ requires C,69.5; H,6.15%.

Hydrolysis of the unsaturated keto-ester.

The unsaturated keto-ester (3.93g.) was added to a solution of potassium hydroxide (1.27g.) in methanol (30 ml.) and the reaction mixture allowed to stand at room temperature for four hours. After evaporation to dryness, the residual solid was dissolved in water, extracted with ether and then acidified to congo red with dilute sulphuric acid. The precipitated oil was extracted into ether, the

ethereal extracts washed with water, dried and the solvent removed to give an oil which solidified on standing. The crude unsaturated keto carboxylic acid (2.46g.) crystallised from a small volume of ethyl acetate in stout prisms, m.p. 98-102° (decomp.). Found: C,63.4; H,7.05; $C_{11}H_{14}O_3$ requires C,63.0; H,7.25%.

Thermal decarboxylation of the unsaturated keto carboxylic acid.

The unsaturated keto-acid (2.06g.) was placed in a flask fitted with a reflux condenser and immersed in an oil bath held at 120-140° for ninety minutes. The cooled reaction mixture was dissolved in ether, and washed with a saturated sodium carbonate solution, water and dried. Removal of the solvent furnished a mixture of the conjugated and non-conjugated unsaturated ketones which could not be separated by fractional distillation, b.p. 102-108°/15 mm., n_D^{19} 1.4978-1.5061.

The infra-red spectrum (liquid film) of this material exhibited maxima at 1710 cms^{-1} (six-membered ring ketone) and 1660 cms^{-1} (conjugated six ring ketone). The ultra-violet absorption spectrum showed a maximum at 252 mμ(ε=6,800).

This mixture gave a dark-red 2:4-dinitrophenylhydrazone (in quantitative yield) which crystallised from ethyl alcohol in plates, m.p. 172-174°. Found: C,57.95; H,5.30; N,16.9. $C_{16}H_{18}O_4N_4$ requires C,58.15; H,5.50; N,16.95%. (λmax in chloroform 390mμ, ε = 11,400).

Hydrogenation of the mixture of conjugated and non-conjugated unsaturated ketones.

The mixture of ketones obtained above (0.8g) was hydrogenated in ethyl acetate (10 ml.) over palladium-charcoal (10%); uptake 13 ml. hydrogen. The reaction mixture was then filtered and evaporated on a steam-bath to

furnish a single product , b.p. 108°/15 mm. $n_D^{25°}$ 1.4712 which exhibited a single maximum in the infra-red at 1705 cm^{-1} (cyclohexanone) and was transparent in the ultra-violet.

The corresponding yellow 2:4-dinitrophenylhydrazone crystallised from methanol in needles m.p. 118.5°-120°. Found; C,58.20; H,5.90; N, 17.0. $C_{16}H_{20}O_4N_4$ requires C,57.80; H,6.05; N,16.85%.

Treatment of 1-carbethoxy-4-hydroxy-3-methylbicyclo (3:3:1) nonan-2-one with furfural.

A sample of the hydroxy keto-ester in ethanol was warmed on a steam-bath for thirty minutes with furfural and aqueous sodium hydroxide (2 ml.4N). The reaction mixture was then evaporated to dryness, the residual solid dissolved in water and extracted with ether. The ethereal extracts, after washing with water and drying, were evaporated to dryness and the residual oil chromatographed on alumina (grade I). Chloroform elution yielded a viscous oil which exhibited a maximum in the ultra-violet at 320 mμ (ε: 2,700). It was impossible to separate the pure furfurylidene derivative from this oil.

2-Allyl-2-carbethoxy-6-methylcyclohexanone (63).

A mixture of 2-carbethoxy-6-methylcyclohexanone (184g.) and allyl bromide (139g.) was added dropwise to a vigorously stirred solution of sodium (23g.) in anhydrous ethanol (600 ml.) held at room temperature. After stirring for three hours, the intermediate thick paste dissolved to give a homogeneous solution. Most of the ethanol was then removed under reduced pressure, and the reaction mixture diluted with water and acidified with concentrated hydrochloric acid. This aqueous solution was then thoroughly extracted with ether and the combined ethereal extracts

washed exhaustively with an aqueous sodium hydroxide solution (10%), water and then dried. Removal of the solvent followed by fractional distillation of the residual oil, furnished 2-allyl-2carbethoxy-6-methyl-cyclohexanone (160g.) as a water-clear liquid, b.p. 88-90°/0.35 mm., $n_D^{21°}$ 1.4659. Found; C,69.2; H,8.7. $C_{13}H_{20}O_3$ requires C,69.6; H,9.0%.

The infra-red spectrum (liquid film) exhibited maxima at 3050 cm^{-1} and 1630 cm^{-1}.

(1-Carbethoxy-2-keto-3-methyl) cyclohexylacetaldehyde (64).

Ozone (flow rate 40 ml/min.) was passed through a solution of 2-allyl-2-carbethoxy-6-methylcyclohexanone (30g.) in methylene chloride (300 ml.), held at -50°, for seven hours. Zinc dust (2.4g.) and aqueous acetic acid (40 ml. 50%) were then added and most of the methylene chloride removed under reduced pressure. The resulting solution was steam distilled and formaldehyde (identified as the 2:4-dinitrophenyl-hydrazone) was isolated from the distillate. The non-steam volatile fragment was then extracted into ether, and the ethereal extract washed with water and dried. Removal of the solvent furnished a thick oil which on distillation gave the required aldehyde (14g.) b.p. 98°/0.1 mm., $n_D^{21°}$ 1.4699. Found; C,63.35; H,8.2. $C_{12}H_{18}O_4$ requires C,63.7; H,8.0%.

The corresponding bis-2:4-dinitrophenylhydrazone crystallised from benzene-petroleum ether (60-80°) in yellow needles, m.p. 195-197°. Found; C,49.55; H,4.35; N,18.7. $C_{24}H_{26}O_{10}N_8$ requires C.49.10; H,4.45; N, 19.1%

Attempted cyclisations of (1-carbethoxy-2-keto-3-methyl) cyclohexylacet-aldehyde (64).

1.) A solution of the aldehyde (2.5g.) in dioxan (25 ml.) was added dropwise to a refluxing solution of dilute hydrochloric acid (5ml., 6N)

in dioxan (20 ml.) and the reaction mixture refluxed for a further hour. The solution was then concentrated to small bulk under reduced pressure and made alkaline with sodium carbonate. The precipitated oil was extracted into ether and the combined ethereal extracts washed with water and dried. Removal of the solvent furnished a gum which could not be purified.

11.) The above reaction conditions were repeated at 45° but no cyclisation was detected.

111.) A mixture of the aldehyde (2.25g.), glacial acetic acid (9.6 ml.), concentrated hydrochloric acid (2.4 ml.) and water (4.8 ml.) was warmed on a steam-bath for a few minutes and then allowed to stand at room temperature for fifteen hours. The reaction mixture was neutralised with solid sodium bicarbonate and then concentrated under reduced pressure. The residual solution was extracted with ether and the ether extracts washed with water and dried. Removal of the solvent furnished the starting aldehyde.

1V.) The conditions described in (111) were repeated but the mixture was refluxed for three hours. When this reaction mixture was worked up, only a polymeric gum was isolated.

V.) The aldehyde (5g.) was added dropwise with stirring to ice-cold concentrated sulphuric acid (12 ml.). After standing for five hours, the red reaction mixture was added to ice-water (30 ml.) and thoroughly extracted with ether. The ethereal extracts were washed with water to pH7, then dried and evaporated. The resultant gum could not be purified either by chromatography on alumina or by high-vacuum distillation.

1-Carbomethoxy-6-hydroxyl-5-methylbicyclo (3:2:1) octan-8-one (65, R= CH_3).

A suspension of the aldehyde (12g.) in aqueous sodium hydroxide (100 ml. 8%) was shaken for eighteen hours at room temperature and then extracted with ether to remove the neutral starting material (0.23g.) The alkaline solution was acidified* to congo red with concentrated hydrochloric acid and extracted with ether. The combined ethereal extracts, after washing with water and drying, were evaporated to dryness and the residual oil esterified with diazomethane. The crude liquid methyl ester (1g.) was distilled, b.p. 122°/0.09mm., and on standing deposited a small amount of crystalline material. Trituration with ether/petroleum-ether (40-60°) furnished solid 1-carbomethoxy-6-hydroxy-5-methylbicyclo (3:2:1) octan-8-one (0.06g.) which crystallised from petroleum-ether (60-80°) in needles m.p. 114-116°. Found; C,62.15; H,7.25. $C_{11}H_{16}O_4$ requires C,62.25; H,7.6%.

The infra-red absorption spectrum (nujol mull) showed maxima at 3440 cms^{-1} (hydroxyl) 1735 cms^{-1} (carbomethoxy) and 1705 cms^{-1} (cyclohexanone).

The corresponding p-toluenesulphonate crystallised from petroleum ether (40-60°) in plates m.p. 85-87°. When the aqueous acidic solution* was constantly ether extracted, the ethereal layer yielded crude 6-hydroxy-5-methylbicyclo (3:2:1) octa-8-one-1-carboxylic acid (4g.) which crystallised from ether in stout needles m.p. 155-157°. Found; C,60.7, H,6.65. $C_{10}H_{14}O_4$ requires C,60.6; H,7.1%.

The corresponding methyl ester was prepared b.p. 112-114°/0.05 mm.

The corresponding para-toluenesulphonate crystallised from ethanol in needles m.p. 146°. Found; C,58.75; H,6.3. $C_{18}H_{22}O_6S$ requires C,59.0; H,6.05%.

1-Carbomethoxy-5-methylbicyclo (3:2:1) octane-6:8-dione (66).

Chromium trioxide (0.1g.) in pyridine (1.5 ml.) was added to a solution of 1-carbomethoxy-6-hydroxy-5-methylbicyclo (3:2:1) octane-8-one, liquid isomer, (0.1g.) and the reaction mixture stirred at room temperature overnight. After pouring into ice-water, the reaction mixture was thoroughly extracted with ether and the combined ethereal extracts washed successively with water, dilute hydrochloric acid, water and then dried. Removal of the solvent furnished the required dione (0.07g. 70%) which crystallised from petroleum-ether (60-80°) in needles m.p. 102-103°. Found; C,63.30; H,6.65. $C_{11}H_{14}O_4$ requires C,62.85; H,6.7%.

The infra-red spectrum (carbon tetrachloride solution) exhibited maxima at 1780; 1749 and 1733 cms^{-1}.

The same diketone was obtained on oxidation of the solid hydroxy keto-ester isomer.

1-Carbomethoxy-6-chloro-5-methylbicyclo (3:2:1) octane-8-one (69).

A solution of phosphorus oxychloride (0.05 ml.) in pyridine (0.5 ml.) was added to a solution of the liquid hydroxy keto-ester, (65, 0.1g.) in pyridine (0.5 ml.) and the reaction mixture after standing overnight at room temperature, poured into ice-cold dilute hydrochloric acid. The reaction mixture was then extracted with ether, and the combined ethereal extracts washed with dilute sodium bicarbonate solution, water and dried. Removal of the solvent furnished a viscous oil which solidified on cooling. 1-Carbomethoxy-6-chloro-5-methylbicyclo (3:2:1) octane-8-one thus isolated crystallised from petroleum-ether (60-80) in plates m.p. 73-75°. Found; C,57.0; H,6.3, Cl.15.2. $C_{11}H_{15}O_3Cl$ requires C,57.35; H,6.5; Cl,15.35%.

The

The same chloro-compound was obtained when the isomeric crystalline alcohol was treated as above.

1-Methyl-3-hydroxy-4-carbomethoxycycloheptanoic acid lactone (67).

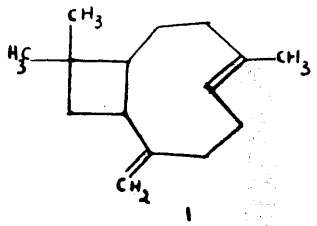
A solution of the liquid alcohol (65, 1.26g.) in concentrated sulphuric acid was stirred at 0° overnight, then poured into ice-water and extracted with ether. The combined ethereal extracts were washed with water, dried, and the solvent removed to furnish the lactone (67, 0.48g.) which crystallised from petroleum-ether (60-80°) in plates m.p. 102-103°. Found; C,62.80; H,7.45. $C_{11}H_{16}O_4$ requires C,62.25; H,7.6%.

The infra-red spectrum (carbon tetrachloride solution) showed one peak at 1740 cms^{-1}.

4-Methylcyclohept-1-ene-1:4-dicarboxylic acid (71).

A solution of the above lactone (0.05g.) in methanol (5 ml.) was refluxed with potassium hydroxide (0.027g.) for three hours and then evaporated to dryness. The residual solid was dissolved in water, extracted with ether, and then acidified to congo red with concentrated hydrochloric acid. The acidic solution was extracted with ether, and the ether extracts washed with water, dried, and the solvent removed under reduced pressure. The residual solid (0.03g.) crystallised from benzene to give the dicarboxylic acid as needles m.p. 175-177°. Found; C,60.70; H,7.0. $C_{10}H_{14}O_4$ requires C,60.60; H,7.10%.

The infra-red spectrum (nujol mull) showed maxima at 3200-2600 cm^{-1} (carboxyl) 1705 cms^{-1} with a shoulder at 1700 cms^{-1}.



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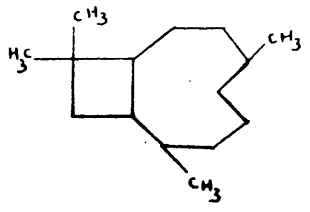

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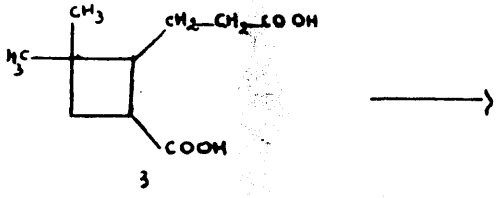

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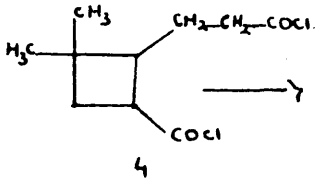

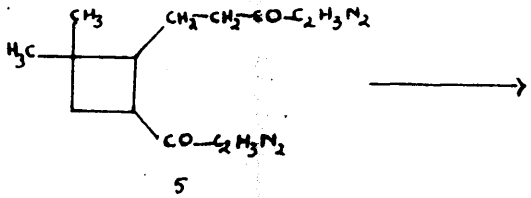

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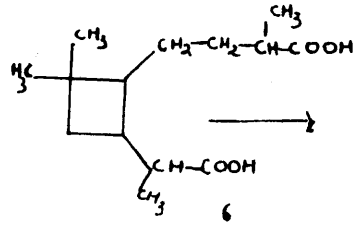
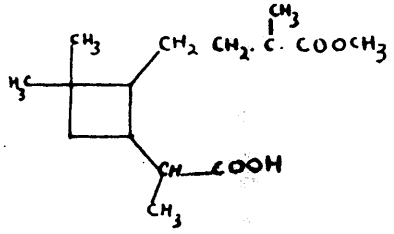
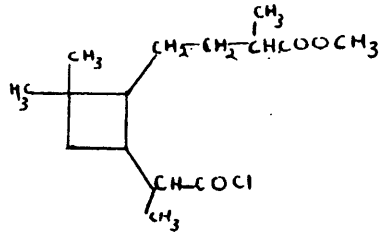
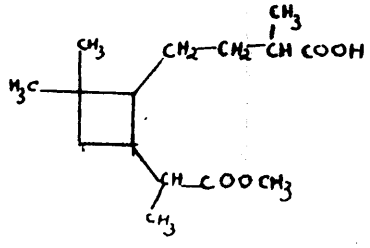
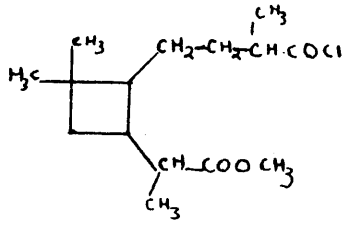


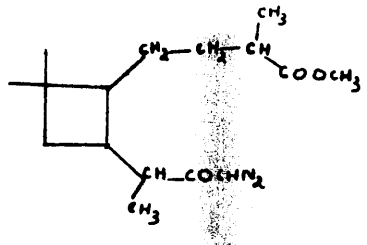


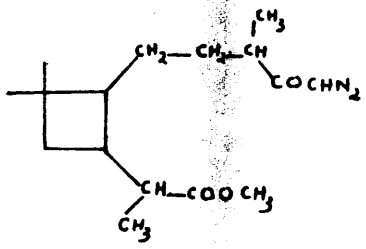
7 a, b. → 8 a, b.











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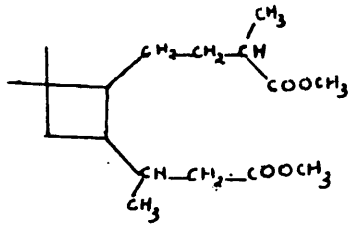

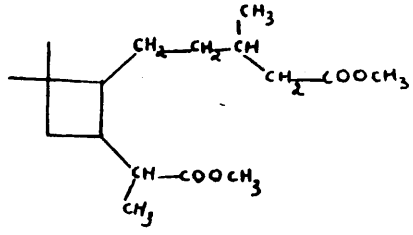

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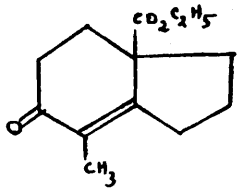

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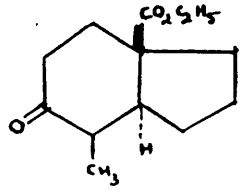

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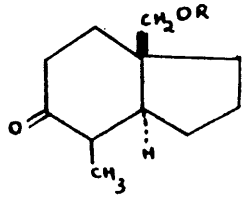

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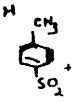
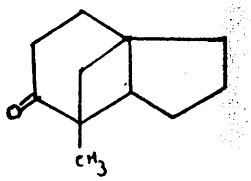
14, R = 



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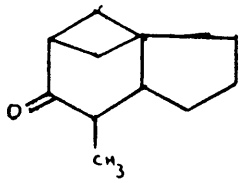

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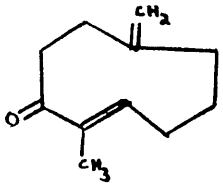

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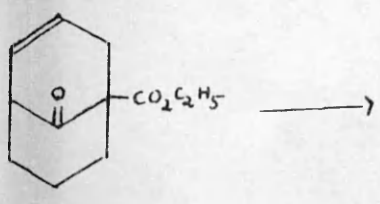

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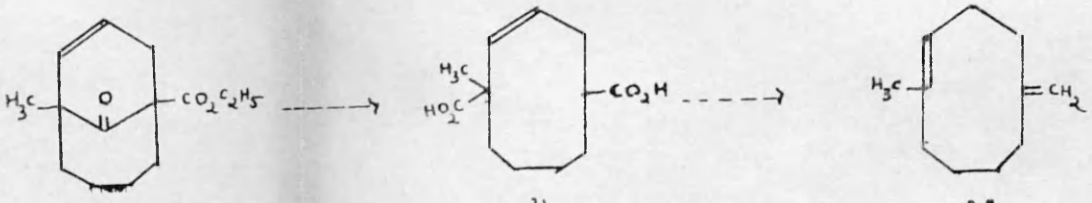

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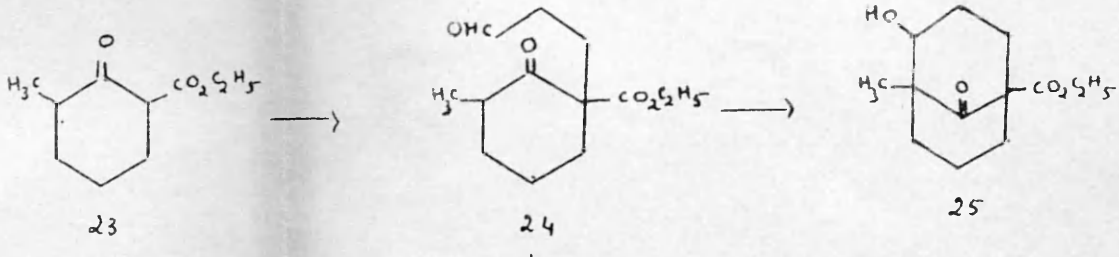

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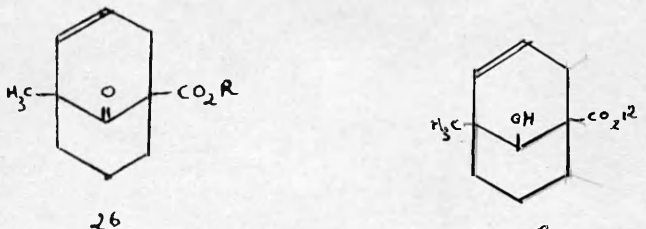

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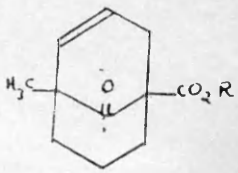

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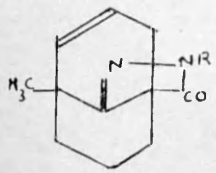

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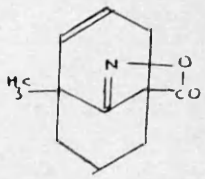

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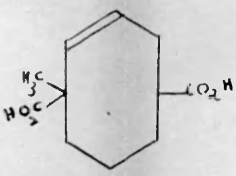

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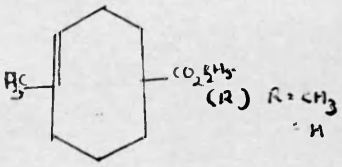

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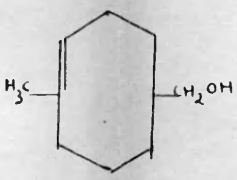

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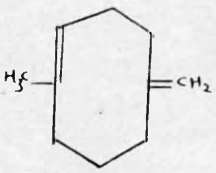

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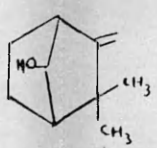

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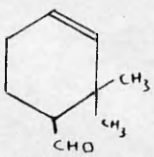

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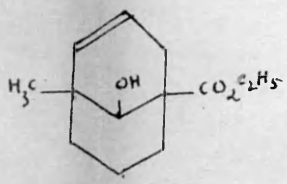

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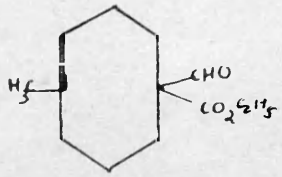

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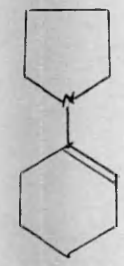

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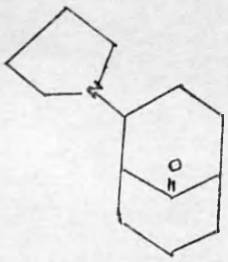

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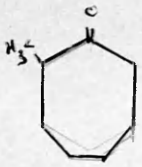

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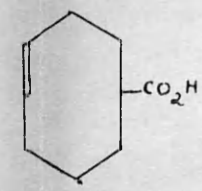

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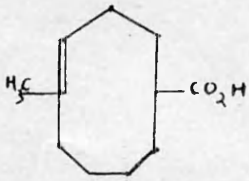

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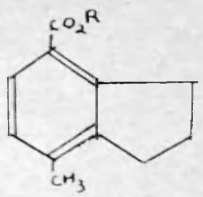

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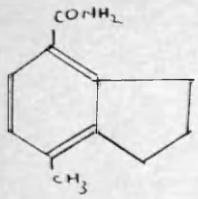

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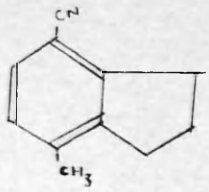

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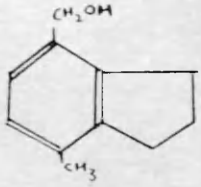

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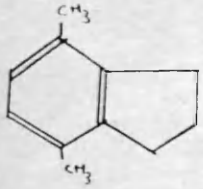

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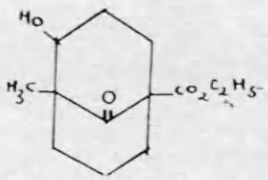

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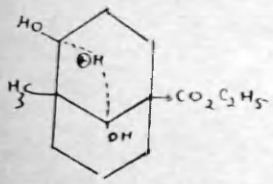

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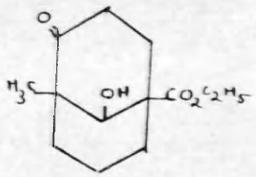

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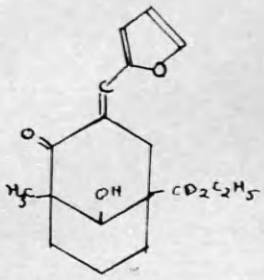

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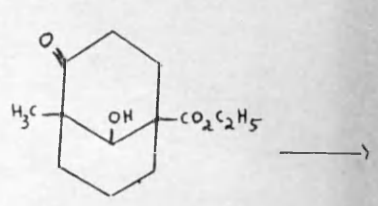

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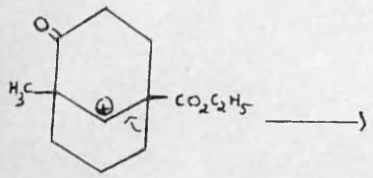

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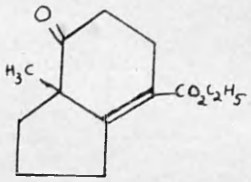

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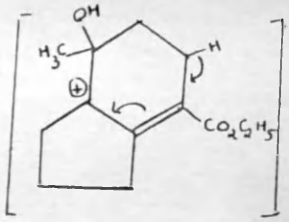

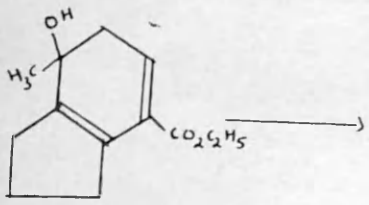

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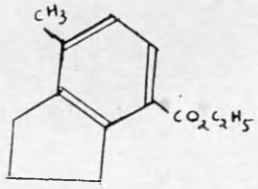

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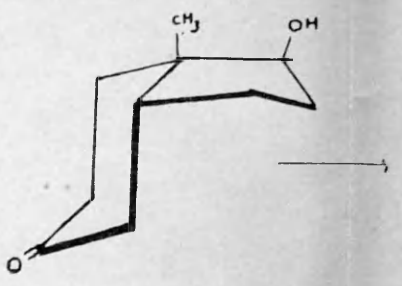

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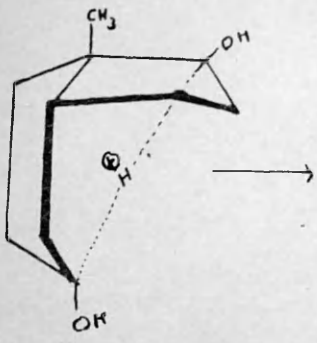

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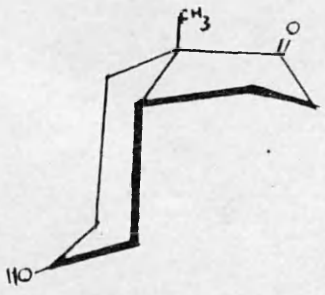

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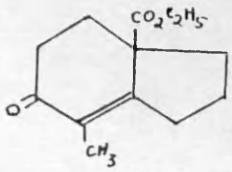

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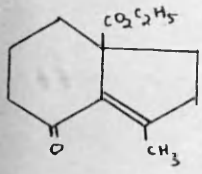

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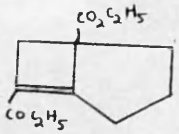

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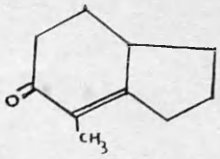

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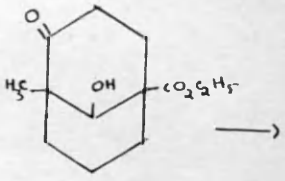

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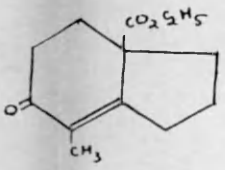

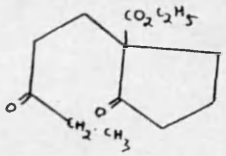

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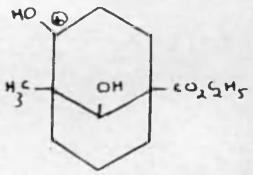

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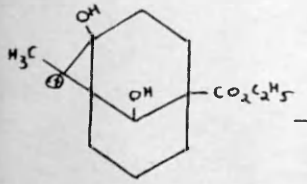

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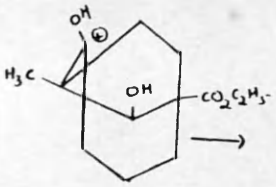

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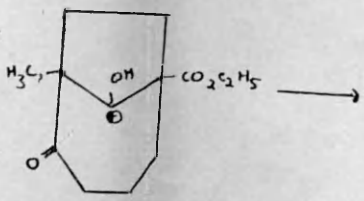

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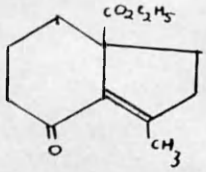

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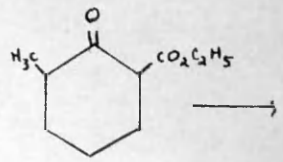

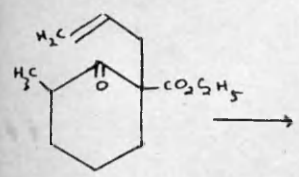

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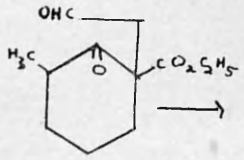

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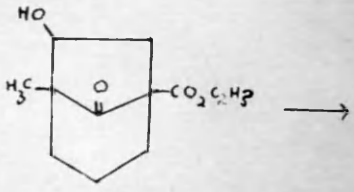

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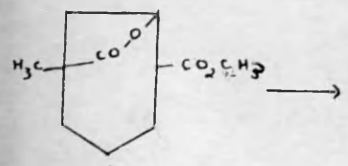

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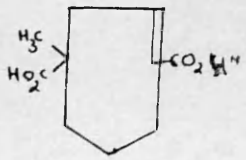

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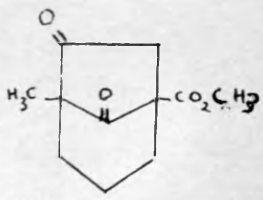

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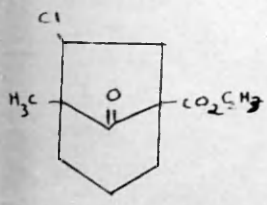

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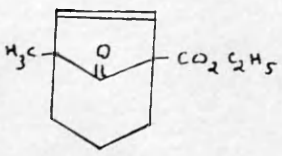

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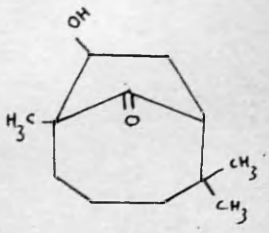

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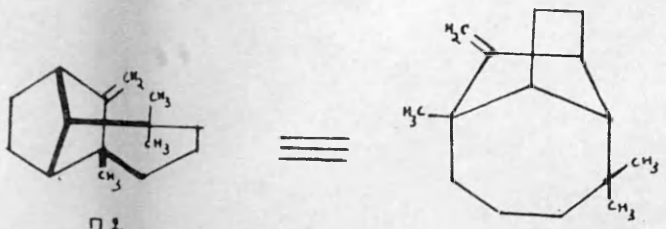

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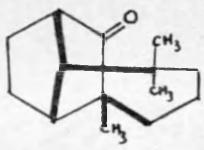

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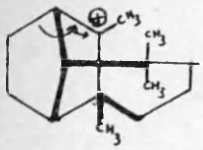

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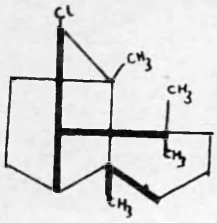

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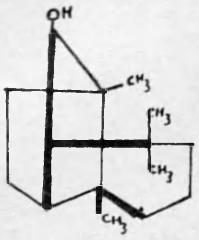

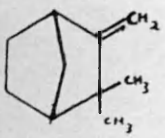

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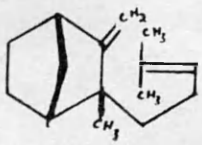

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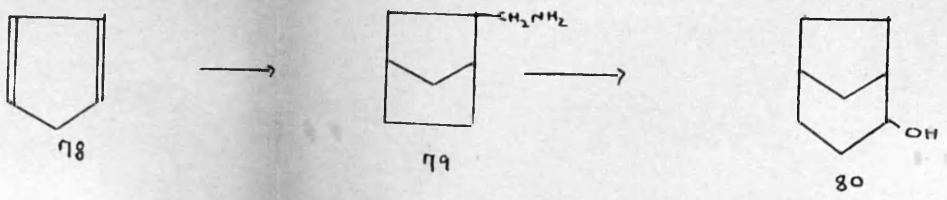

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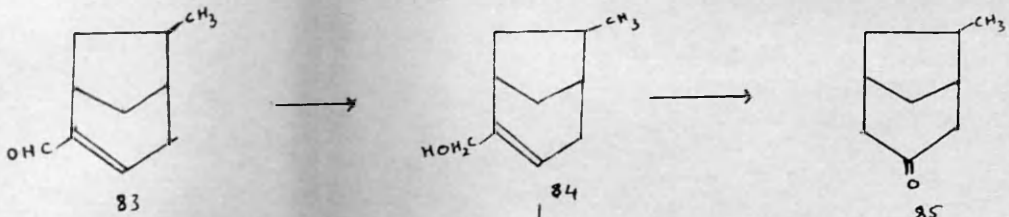

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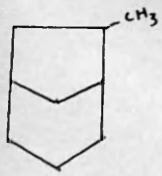

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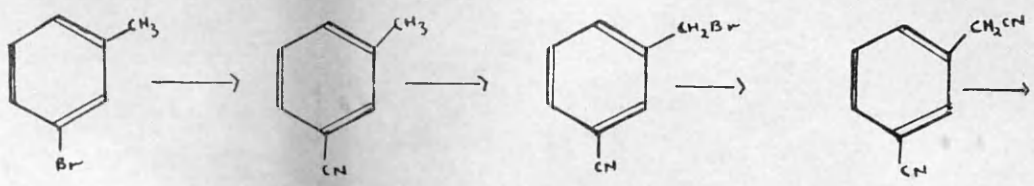
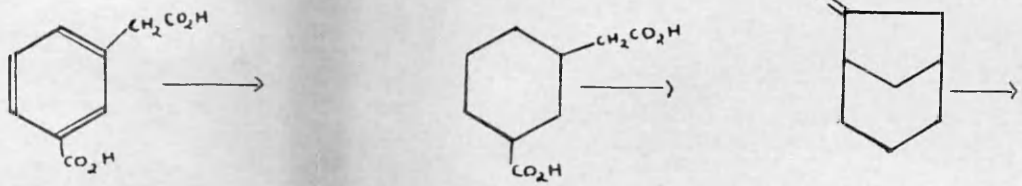
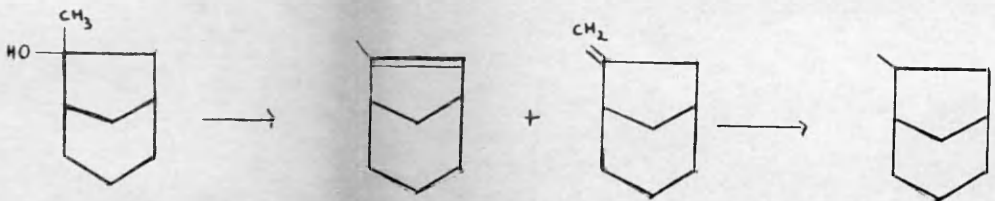
Scheme A







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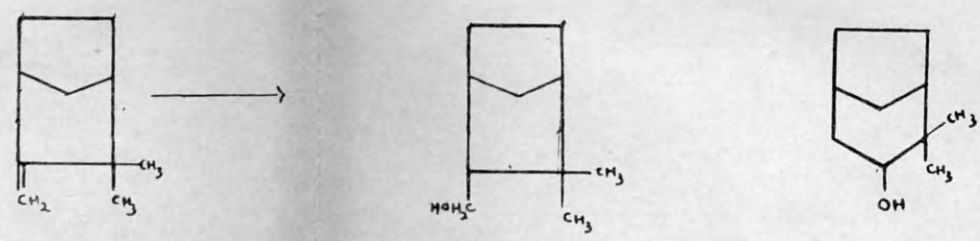

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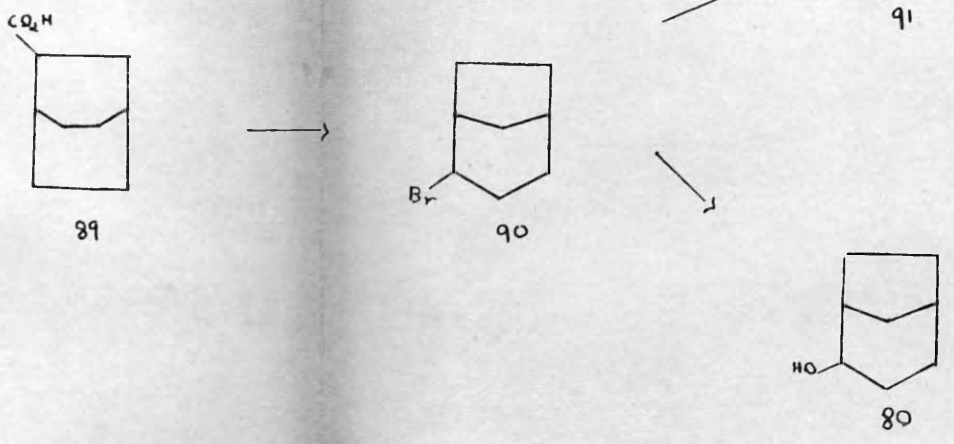

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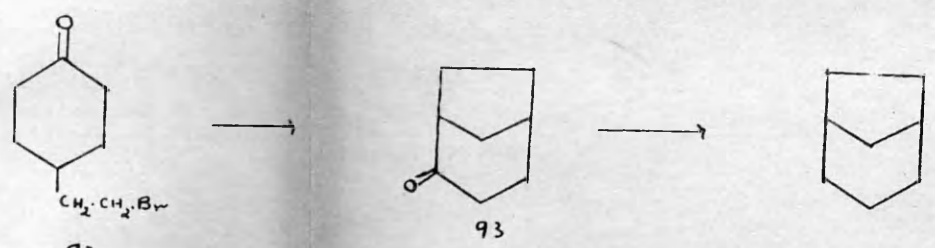

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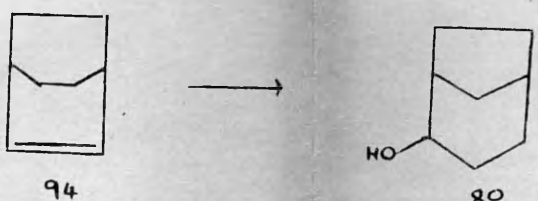

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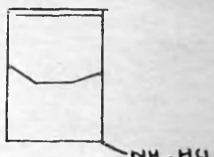

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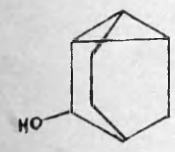

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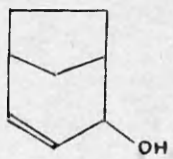

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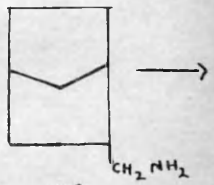

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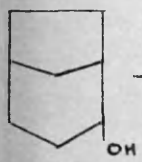

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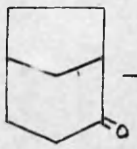

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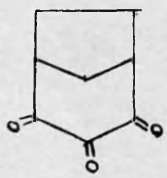

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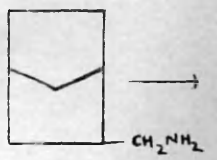

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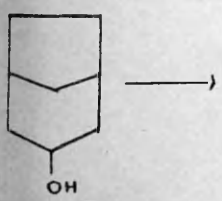

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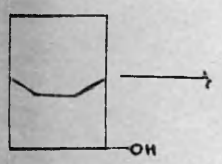

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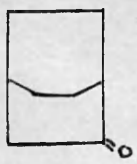
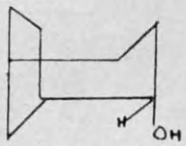
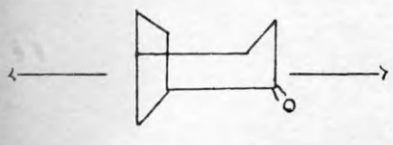
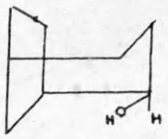


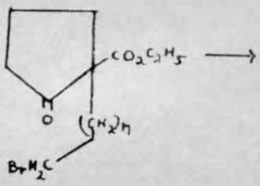


Trans - axial





Cis - equatorial



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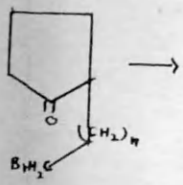

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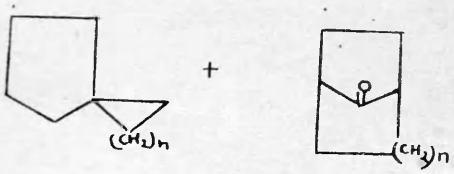

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107 108

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